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STUDIES OF SEX HORMONES IN ACNE

I. PRELIMINARY REPORT ON URINARY EXCRETION OF ESTROGEN

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The etiology of acne vulgaris is still obscure. Numerous factors, such as seborrhea, bacterial infection, disturbances of carbohydrate and fat metabolism and the ingestion of certain halogens and foods, have all been assumed to be of importance in individual cases. However, at the present time these are considered secondary, and there is still no adequate explanation for the causation of the disease.

Acne is strikingly a disease of adolescence and has occasionally been associated clinically with disturbances of the endocrine system, especially of the gonads. Bloch,[1] in a study of over 4,000 school children, has shown a close correlation between the development of acne and the appearance of physical evidences of sexual development. His figures show acne to be most common in girls at the age of 17 and in boys at the age of 18. It is also well known that in women exacerbations of the eruption are frequently associated with various phases of the normal menstrual cycle, and in innumerable cases acne is associated with some menstrual disorder.

Experimental verification of these interesting relations has been forced to await the development of quantitative methods of determination of estrogen and of androgen. In 1933 Rosenthal and Kurzrok[2] studied the urinary output of estrogens of normal women and of women with acne. They found in general a diminished amount for

From the Department of Dermatology and Syphilology, service of Dr. U. J. Wile, and the Department of Gynecology and Obstetrics, service of Dr. Norman F. Miller, University of Michigan Medical School.

1. Bloch, B.: Endocrine Glands and Skin Diseases with Special Reference to Acne Vulgaris, Brit. J. Dermat. **43**:61, 1931.

2. Rosenthal, T., and Kurzrok, R.: Excretion of Estrin in Acne, Proc. Soc. Exper. Biol. & Med. **30**:1150, 1933.

persons with acne. In 1935 Rosenthal and Neustaedter [3] reported a diminished amount of estrogenic substance in the blood in women with acne. In 1936 McCarthy and Hunter [4] undertook the study of the amounts of estrogenic and gonadotropic substances in the blood. They interpreted their findings as indicating a deficiency of function of the anterior lobe of the pituitary or of the gonads in a considerable number of persons with acne.

The present study was undertaken to verify and extend previous studies of the possible relation of estrogen and of androgen to acne.

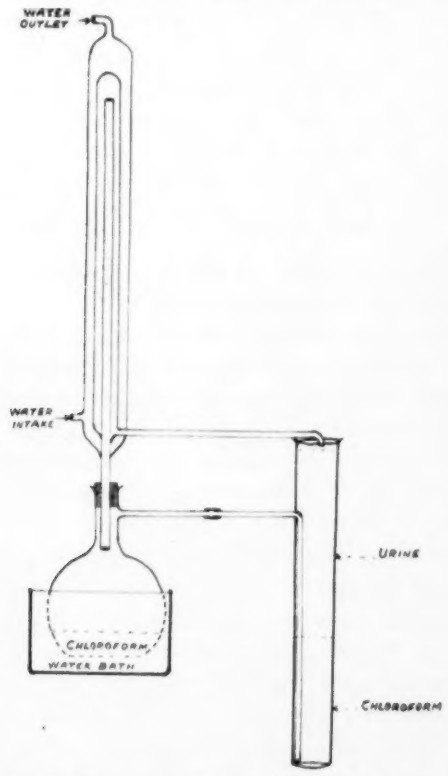

Fig. 1.—Apparatus used for extraction of estrogenic substance.

We have employed somewhat different methods and have controlled several factors which have been found to be of considerable importance in such steps as (1) the collection of specimens of urine at a definite time in the menstrual cycle and (2) the utilization of a larger series of experimental animals for each assay.

3. Rosenthal, T., and Neustaedter, T.: Estrogenic Substance in the Blood of Patients with Acne, Arch. Dermat. & Syph. **32**:560 (Oct.) 1935.

4. McCarthy, L., and Hunter, O. B.: Failure of Therapy with Glandular Preparations in Acne Vulgaris, Arch. Dermat. & Syph. **35**:211 (Feb.) 1937.

TECHNIC

The method employed for the determination of estrogenic substance in the urine was as follows: Twenty-four hour specimens were collected during the mid-interval of the menstrual cycle. The specimen was acidified by the addition of 10 cc. of concentrated hydrochloric acid per liter of urine.[5] Seven hundred and fifty cubic centimeters of the acidified specimen was utilized in extraction.

The extraction apparatus was copied after that of Frank and Goldberger.[6] Their graduate cylinder was replaced by a cylinder into which the return tube had been fused at a level which would insure a return flow of the chloroform (fig. 1). The condenser was designed for rapid distillation and had the advantage of being compact. About 250 cc. of chloroform was put into the cylinder, and then 750 cc. of urine was added. The excess chloroform was displaced into the distilling

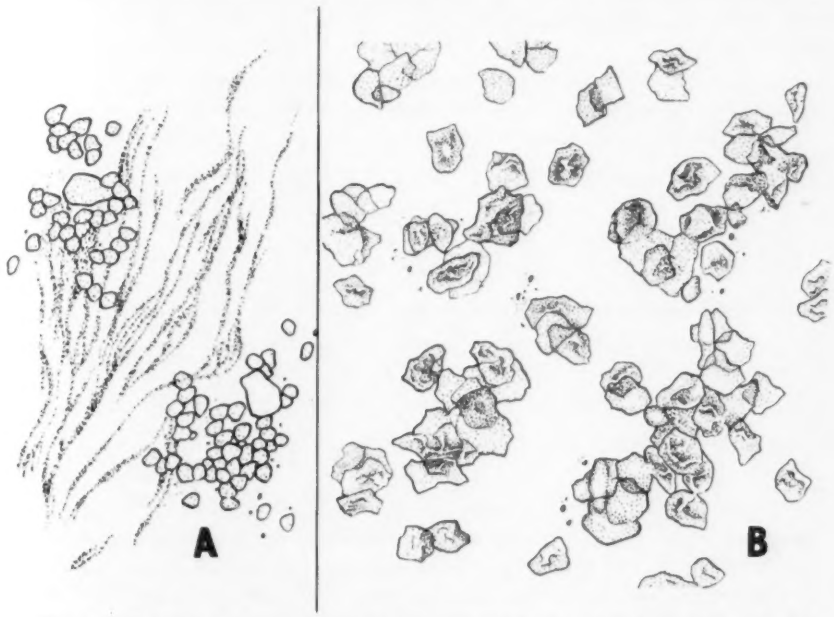

Fig. 2.—Example of estrus response of castrated rat; drawings of smears of vaginal contents before (*A*) and after (*B*) injection of estrogenic substance.

flask, and the distillation was started. The system was entirely closed except at the point where the chloroform dropped into the urine; so there was relatively little loss of the extracting agent.

5. This work was done in 1935-1936, before it was realized that the estrogenic materials were not completely recovered at this relatively low degree of acidity. We now consider these values as representing the free rather than the total estrogenic substance. The total estrogenic substance has been determined in our subsequent work.

6. Frank, R. T., and Goldberger, M. A.: The Female Sex Hormone: VIII. Simplification of Technic, J. A. M. A. **90**:376 (Feb. 4) 1928. Frank, R. T.: The Role of the Female Sex Hormone, ibid. **97**:1852 (Dec. 19) 1931.

After twenty-four hours of continuous distillation the urine was discarded and the residue from the chloroform extract was taken up in 3 cc. of olive oil. The olive oil solution was assayed on castrated female rats.

The assay animals were young albino rats that had undergone bilateral oophorectomy under chloroform-ether anesthesia. Two weeks postoperatively the taking of daily vaginal smears was started; this was continued for two or three weeks to determine whether castration was complete. The absence of any cornified cells in the vaginal smear during this period was considered proof of complete castration. Injection of estrogenic substance into castrated rats produces a marked proliferation and cornification of the vaginal mucosa. These changes are readily determined by a microscopic examination of a sample of the vaginal contents obtained by a small wire loop (fig. 2). The amount of urinary extract necessary to produce cornification of the vaginal mucosa thus affords a quantitative method of determining the estrogen content of the original specimen of urine.

Urinary Excretion of Estrogen by Women

Normal Women				Women with Acne	
Case No.	R.U. per 1,000 Cc.	Case No.	R.U. per 1,000 Cc.	Case No.	R.U. per 1,000 Cc.
1	7	11	8	1	3
2	5	12	7	2	4
3	12	13	9	3	3
4	6	14	8	4	4
5	9	15	6	5	4
6	6	16	8	6	4
7	9	17	7	7	4
8	6	18	8	8	4
9	9	19	10	9	4
10	7	20	7	10	4
				11	4
				12	7
Average			7.7		4.1

In this study the urinary extracts in olive oil were injected into 3 rats on two successive days. Vaginal smears were examined for the next three days. As the concentration of the extract was unknown, the approximate range had to be determined by trial and error. For example, if all rats responded positively to the first trial, the assay was repeated with half the original dose. Only when at least 2 of the 3 rats showed positive estrus smears was the test considered positive with that dose. The rats were given at least one week's rest between assays.

RESULTS

The results are given in the table. For the series of 20 normal young women the urinary output of estrogen varied between 5 and 12 rat units per liter, with an average value of 7.7 rat units per liter. The urinary output of estrogen in a group of 12 young women with severe acne varied between 3 and 7 rat units per liter, with an average value of 4.1 rat units per liter of urine. There was some overlapping of the values for the normal women and those with acne, but in general the values were lower for the latter group.

COMMENT

In view of the clinical facts which seem to establish acne as a disease definitely related to sexual development, the finding of a marked diminution of estrogen in the urine of women with acne would at first glance appear paradoxic, especially since acne vulgaris does not ordinarily occur during the preadolescent period, in eunuchoid states and in senility.

However, because of the complex interrelationship of the various endocrine glands, the interpretation of results confined to a single hormone is difficult, and conclusions must be drawn with caution. Consideration, for instance, of the facts that each woman excretes not only estrogen but a certain amount of androgen and that these two substances are interrelated in their action makes it apparent that any study of the relation of the substances to acne should include a consideration of the androgenic as well as the estrogenic substances. In the study to follow we have broadened the attack on this interesting problem by making simultaneous determinations of the excretion of androgen and of estrogen by men and women with and without acne.

SUMMARY

For a series of 20 normal young women between the ages of 15 and 21 the urinary output of estrogen was found to average 7.7 rat units per liter.

For a similar series of 12 young women with severe acne the urinary output of estrogenic substance was found to average 4.1 rat units per liter.

In general, there is a diminution in the urinary excretion of estrogen by young women with acne vulgaris.

STUDIES OF SEX HORMONES IN ACNE

II. URINARY EXCRETION OF ANDROGENIC AND ESTROGENIC SUBSTANCES

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We presented previously the results of our investigations on the output of estrogen in the urine of a group of normal women, as compared with that of a group of women of the same age with acne. From this study we were able to show that the women with acne excreted considerably less estrogen than did the normal women.

As acne is even more frequent in men, it was obviously necessary to project our studies further by the determination of the output of androgen for a group of men with acne, as compared with that of a group of normal men of the same age. Furthermore, as the gonadal activity of persons of each sex is expressed by the excretion of both androgen and estrogen in measurable amounts, we decided to broaden our study to include simultaneous determinations of the urinary excretion of both substances in each case. In other words, to study adequately the problem of the relation of androgen and estrogen to the causation of acne, it became necessary to make determinations of the output of both estrogen and androgen in persons of both sexes with the disease, after having established values for these substances in groups of normal men and women of the same age.

EXPERIMENTAL METHODS

In each case the total urinary output for two days was carefully collected and pooled. Half of this amount was taken as an average twenty-four hour specimen. For women the samples were collected between the tenth and the eighteenth day after the onset of the last menstrual period.

The twenty-four hour specimen was measured and the specific gravity noted. The estrogen and the androgen in the entire specimen were extracted and assayed. It will be noted that in the preceding study we expressed the amount of estrogen in units per liter of urine, irrespective of the volume excreted during the day,

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whereas in the present study we have determined the total amount of the substances excreted per twenty-four hours. We have also used an entirely different method of extraction.

For the extraction of the substances we have used the recently perfected method of Gallagher, Koch and Dorfman.[1] This permits the complete extraction of both the androgen and the estrogen from the same specimen of urine. The two substances were then separated and assayed independently. The estrogen was assayed by the production of estrus in spayed rats. The androgen was assayed by the amount of growth produced in the combs of capons, according to the method of Gallagher and Koch.[2]

Technic of Extraction.—The twenty-four hour specimen of urine was acidified by the addition of 100 cc. of concentrated commercial hydrochloric acid per liter of urine, boiled for fifteen minutes and cooled.[3] The complete sample was then placed in the special Koch extraction apparatus and extracted with 10 volumes of benzene. This apparatus permits the intimate contact of the urine with a fine spray of benzene bubbles, which rise continuously through a 4 foot (120 cm.) column of the urine for about eight hours. This produces complete extraction of all the androgen and estrogen. A diagram of the extraction apparatus is shown in figure 1.

The benzene containing the substances was then distilled off and the residue dissolved in 75 cc. of ether. To separate the androgen from the estrogen this ether solution was then shaken with ten separate washings of 10 per cent aqueous solution of sodium hydroxide. The estrogen, being soluble in the alkali, was removed by these washings, while the ether retained the androgen.

Assay of Androgen.—The ether solution containing the androgen was washed with distilled water and mixed with 26 cc. of olive oil. The ether was then completely distilled off under reduced pressure, to leave the androgen in the olive oil. The residue was then assayed for androgen.

A flock of white leghorn cockerels were caponized at about 2 months of age and kept until they had attained full growth. They were then housed indoors in subdued light and were at no time exposed to sunlight.[4] Five capons were used in each determination, and assays were made at intervals of one month on each group of birds. In order to insure comparable conditions, determinations were made each month on samples of urine from both normal persons and patients with acne, and a given group of capons received a specimen from a normal person one month and a specimen from a patient with acne the following month.

Each capon received an injection of 1 cc. of the solution of androgen in oil into the pectoral muscles daily for five days. The height and length of the comb were carefully measured in millimeters on the first and again on the sixth day. After the necessary correction for initial comb length was made in each instance

1. Gallagher, T. F.; Koch, F. C., and Dorfman, R. L.: Procedure for Quantitative Extraction of Sex Hormones from Urine, Proc. Soc. Exper. Biol. & Med. **33**:440, 1935.

2. Gallagher, T. F., and Koch, F. C.: The Quantitative Assay for the Testicular Hormone by the Comb-Growth Reaction, J. Pharmacol. & Exper. Therap. **55**:97, 1935.

3. Peterson, D. H.; Gallagher, T. F., and Koch, F. C.: The Effect of Acid Hydrolysis on the Yield of Androgenic and Estrogenic Activities from Human Urine, J. Biol. Chem. **119**:185, 1937.

4. Koch, F. C.: Some Factors Affecting the Comb-Growth Response in Leghorn Capons, J. Pharmacol. & Exper. Therap. **41**:173, 1931.

the average increase in height plus length for each assay group of birds was determined. This was then compared with the standard curve of values established by Gallagher and Koch and transposed into capon units. Examples of the comb growth response of capons to the injection of androgen are illustrated in figure 2.

As originally defined, a capon unit is that amount of androgen which when injected daily for five days gives an average of 5 mm. increase in height and length of the comb of at least 5 of 10 leghorn capons. Recently, however, the international unit of androgen has been defined as a definite amount (0.1 mg.) of

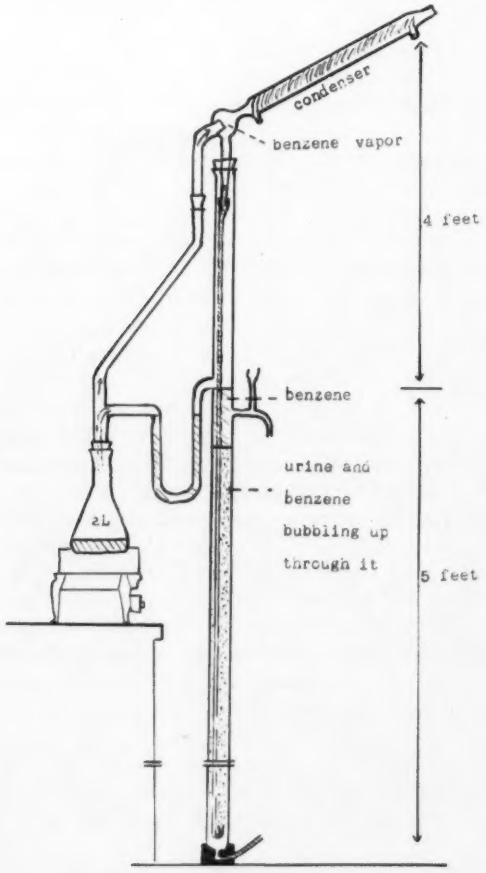

Fig. 1.—Continuous extractor of androgenic and estrogenic substances from urine (Koch and Gallagher).

crystalline androsterone. The relationship of the capon's comb response to a known dose of androsterone has been worked out by Gallagher and Koch and found to follow a characteristic curve. The capon unit (C. U.) used in this paper is therefore approximately equivalent to the international unit (0.1 mg. of androsterone).

Assay of Estrogen.—The combined washings with 10 per cent sodium hydroxide containing the estrogen were acidified with concentrated sulfuric acid. After being

cooled the preparation was shaken with at least three separate 50 cc. portions of ether. The ether washings were then shaken with 10 per cent sodium carbonate to remove the excess acid and some of the extraneous material. The ether was then distilled off and the residue taken up in propylene glycol. This solution was injected into 5 castrated rats on two successive days, and vaginal smears were taken forty-eight, sixty and seventy-two hours after the initial injection. The response of the rats to known doses of theelin (estrone) had been determined previously; so the estrogenic activity of the urinary extracts is expressed in micrograms of crystalline theelin.[5] One rat unit, as used in this paper, is approximately 1 microgram of theelin.

Fig. 2.—Examples of the comb growth response of capons before (*A*) and after (*B*) five days' injection of androgen.

The relationship between the dose and the percentage of animals responding positively was determined in a manner similar to that described by Gustavson and associates.[6] Crystalline theelin in doses varying from 0.5 to 4 micrograms (0.0005 to 0.004 mg.) dissolved in propylene glycol was given to groups of 15 rats each. The percentage of rats responding positively to each dose was plotted and a curve

5. Dr. Oliver Kamm, of Parke, Davis & Co., supplied the theelin.

6. Gustavson, R. G.; Mason, L. W.; Hays, E. E.; Wood, T. R., and D'Amour, E. D.: The Quantitative Determination of Estrogenic Substances in Normal Female Urine During the Menstrual Cycle, Am. J. Obst. & Gynec. **35**:115, 1938.

obtained. Dr. A. C. Lin supplied these data. All assay rats were primed with crystalline theelin a week before they were inoculated with the unknown substance. This was necessary because the first estrus after castration is the most difficult to produce.

The observations herein described were made on 34 patients. These were divided into four groups, as follows: (1) 6 normal men; (2) 9 men with acne; (3) 6 normal women, and (4) 10 women with acne.

All patients were in the same age group, namely from 16 to 21 years. In all the cases the acne was moderately severe or severe. In each case quantitative determinations were made both for androgen and for estrogen.

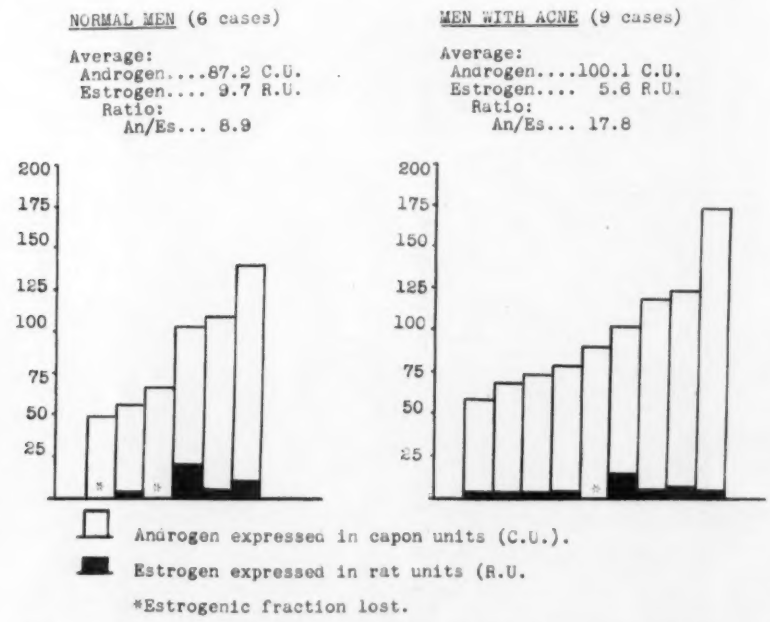

Fig. 3.—The urinary excretion of androgen and of estrogen by men. Cases are arranged arbitrarily in the order of increasing output of androgen.

RESULTS

Men.—The results for the 6 normal men and the 9 men with acne are given in figure 3 and table 1. The urinary excretion of both androgen and estrogen was found to vary considerably in each group. The output of androgen of the normal men ranged from 49 to 140 capon units per day, with an average of 87 C. U. The output of androgen of the men with acne varied from 59 to 176 capon units per day, with an average of 100 C. U.

The twenty-four hour output of estrogen of the men was also found to vary considerably in both groups. The output of the normal men ranged from 4 to 20 rat units per day, with an average of 9.7 rat

units. The excretion of estrogenic substance by the group of men with acne varied from 3 to 15 rat units per day, with an average of 5.6 units.

TABLE 1.—*Urinary Excretion of Androgen and Estrogen by Men*

Case No.	Age	Volume, Cc. per 24 Hr.	Specific Gravity	H + L,* Mm.	C.U.*	R.U.*	An/Es
Normal men							
1	18	3,700	1.008	9.3	65.8	Lost	....
2	17	1,575	1.020	7.8	49.4	Lost	....
3	21	2,600	1.010	13.4	140.4	10	14.0
4	17	1,750	1.012	11.8	108.1	5	21.6
5	17	2,000	1.015	8.5	56.7	4	14.1
6	21	3,000	1.010	12.5	103.2	20	5.1
Average					87.2	9.7	8.9
Men with acne							
10	17	2,400	1.015	11.0	91.0	Lost	....
11	16	1,950	1.012	11.6	103.5	15	6.8
12	16	1,550	1.022	10.4	80.9	4	20.2
13	20	950	1.025	12.6	124.8	7	17.8
14	17	1,150	1.022	15.1	176.8	5	35.3
15	17	2,100	1.017	12.3	120.4	5	24.1
16	17	1,500	1.022	9.6	69.4	3	23.1
17	16	1,400	1.024	10.0	74.9	3	24.9
18	18	1,400	1.020	8.8	59.8	3	19.9
Average					100.1	5.6	17.8

* Here and in table 2 H + L signifies the increase in height plus length of capon's comb; C.U., the amount of androgen expressed in capon units, and R.U., the amount of estrogen expressed in rat units.

TABLE 2.—*Urinary Excretion of Androgen and Estrogen by Women*

Case No.	Age	Volume, Cc. per 24 Hr.	Specific Gravity	Time*	H + L, Mm.	C.U.	R.U.	An/Es
Normal women								
20	21	1,524	1.011	18	6.0	33.8	20	1.7
21	18	1,000	1.016	16	6.6	39.0	20	1.8
22	20	1,760	1.008	18	10.5	80.6	10	8.1
23	16	1,100	1.010	15	7.0	41.8	19	2.2
24	20	975	1.010	14	8.2	53.3	13	4.1
25	19	850	1.010	14	4.0	18.5	15	1.2
Average						44.5	16	2.7
Women with acne								
30	16	1,000	1.025	11	8.7	58.8	5	11.8
31	21	2,900	1.007	15	8.3	54.3	15	3.6
32	20	900	1.015	10	7.5	46.3	10	4.6
33	17	1,600	1.016	16	11.2	94.0	20	4.7
34	20	1,350	1.012	11	5.6	30.4	Lost	....
35	18	1,350	1.012	17	10.1	76.4	13	5.8
36	21	2,300	1.010	12	6.8	40.1	15	2.6
37	19	900	1.020	10	8.0	51.2	5	10 2
38	20	1,900	1.012	12	9.2	64.4	19	3.4
39	18	1,200	1.020	10	8.7	58.7	5	11.7
Average						57.4	12	4.7

* Number of days after onset of last menses.

Women.—The twenty-four hour urinary excretion of androgen and estrogen by 6 normal women and by 10 women with acne is given in figure 4 and table 2. Here it may be seen again that the excretion

of both androgen and estrogen varied considerably in each group. For the normal women the output of androgen ranged from 18 to 80 capon units per day, with an average of 44 capon units. For the women with acne the excretion of androgen varied from 30 to 94 capon units per day, with an average of 57 capon units.

The excretion of estrogens also varied in both groups of women. The normal women were found to excrete from 10 to 20 rat units per day, with an average of 16 rat units, whereas the output for the women with acne ranged from 5 to 20 rat units per day, with an average of 12 rat units.

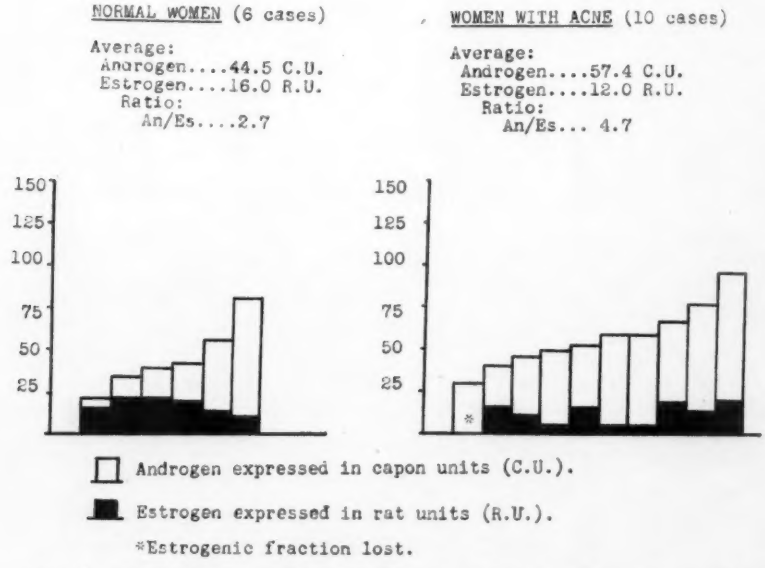

Fig. 4.—The urinary excretion of androgen and estrogen by women. Cases are arranged arbitrarily in the order of increasing output of androgen.

COMMENT ON RESULTS

In quantitative experiments involving bioassay it must be constantly remembered that an experimental error of considerable magnitude is unavoidable even with the best methods available. It has been shown previously by other investigators[7] that there is a large variation from day to day in the excretion of both substances by perfectly normal persons. With these points in mind one should not be surprised that we have been unable to determine any changes which will invariably

7. Gallagher, T. F.; Peterson, R. I.; Dorfman, R. I.; Kenyon, A. T., and Koch, F. C.: The Daily Urinary Excretion of Estrogenic and Androgenic Substances by Normal Men and Women, J. Clin. Investigation **16**:695, 1937.

characterize all patients with acne as compared with normal persons in the same age group. However, if one compares the average values for each group, several interesting points are brought out by the present study.

We have confirmed our earlier findings, that in general the excretion of estrogen is lower for a group of women with acne than for a corresponding group of normal women. The average daily output of the group of women with acne was 12 rat units, as compared with 16 rat units per day for the group of normal women.

The men with acne also excreted less estrogen than did the normal men. The average daily excretion of estrogen by men with acne was 5.6 rat units, as compared with 9.7 rat units for the normal men.

These two results, then, permit us to state that, in general, groups of women and of men with acne excrete less estrogen than do the corresponding normal groups.

The average daily output of androgen was found to be greater for the group of men with acne than for the group of normal men, the average being 100 capon units for the former group, as compared with 87 for the latter.

There was also a difference in the excretion of androgen by the two groups of women, the women with acne excreting appreciably larger amounts than did the normal women. The former group excreted an average of 57 capon units per day, as compared with 44 capon units for the latter.

From these two findings it appears that groups of men and women with acne both excrete more androgen than the corresponding normal groups.

All previous work on the relation of the "sex hormones" to acne has seemed to indicate that acne is due to diminution of these substances. The results of the present studies, which include a determination of androgen as well as of estrogen, indicate that this previous view was erroneous because incomplete. We have found that patients of both sexes with acne excrete larger amounts of androgen than do normal persons of corresponding age. This suggests that the disturbance is not merely one of increase or decrease of a single factor but that a more complex imbalance may be involved.

By simultaneous determination of the excretion of both substances by each person, data have been obtained which enable us to study the ratio of the output of androgen to that of estrogen for each person. This seems worth while because it gives some idea of the relative proportion or balance of the two elements in each person in the group.

The ratio of the daily excretion of androgen to that of estrogen for the normal men was found to be 8.9, whereas for the men with acne it was 17.8, almost twice as great.

For normal women the ratio of daily output of androgen to that of estrogen was 2.7, as compared with 4.7 for the women with acne. Here again the ratio was almost twice as great for the women with acne as for the normal women.

These are significant findings because they indicate that the disturbance of the balance between androgen and estrogen in patients with acne is of a similar nature in both sexes.

CONCLUSIONS

A moderate increase in the urinary excretion of androgen was found in cases of acne in both sexes.

A decrease in the excretion of estrogen was noted for both sexes.

The ratio of excretion of androgen to that of estrogen was found to be almost twice as great for men with acne as for normal men and for women with acne as for normal women.

These findings, however, are based on average values for each group and do not apply to every case. The results would seem to indicate that there is no rationale for the use of androgenic substance in the treatment of acne vulgaris. While it would appear that the diminished excretion of estrogen in many cases of acne would suggest treatment with this substance, we feel that there is not yet sufficient proof of the etiologic significance of this diminution to justify its indiscriminate or empiric use therapeutically.

ABSTRACT OF DISCUSSION

Dr. H. J. Templeton, Oakland, Calif.: For the last several years my associates and I have been interested in the problem of treating acne with various "sex hormone" extracts. We set out with the idea of determining the amount of estrogen in the urine of young nurses living under identical conditions of age, diet and hours of work. We estimated the amount of estrogenic substance in the urine of 2 normal nurses at four different phases of the menstrual cycle and also the amount of the same substance in the urine of 2 nurses who were suffering from rather severe acne (also at four different periods of the menstrual cycle). About that time we ran into the same difficulty that Dr. Wile has mentioned, that is, the tremendous amount of work involved. It took actually two hundred hours of work for each patient, and this was found to be prohibitive. Therefore, that phase of the experiment was dropped. I may say, however, that in our small series of cases we noted no significant variations in the amount of estrogenic substance in the urine of the 2 normal women and in that of the 2 with acne.

Next, we felt that an improvement could be made on the method of analysis of estrogenic substance in the urine. In the usual method of analysis concentrated urine is injected into animals. No one knows how much of the substance is wasted in the metabolism of the individual animal and how much will be excreted per vaginam to produce cornification. A possible variation between animals cannot be controlled. We devised a method of analysis in which we applied the concentrated urine direct to the vaginal mucosa and noted the degree of cornification. This saves a great deal of work, and we believe it is a more

accurate method. Lastly, we attempted to determine the therapeutic effect of the injection of a gonadotropic or an estrogenic substance in patients with acne. We selected 25 university students suffering from acne and photographed them before beginning our experiments, so that we could have a base line of comparison from which to work. In the first series of 25 we injected a gonadotropic substance from the urine of pregnant women (antuitrin S) twice a week for periods varying from twelve to sixteen weeks, which we felt was as long a period as we could ask any patient to try a certain form of treatment. All other treatment was discontinued except the use of soap and water. At the end of the treatment we found that there was no significant improvement in the patients given the injections. True, some of them improved, but no more than might have been expected with far simpler methods of treatment.

The next series of 25 were photographed, and injections of an estrogenic substance (amniotin) were given in the same manner. The results were the same, that is, extremely disappointing.

Dr. George C. Andrews, New York: In corroboration of what Dr. Wile has said, my associates and I have experimented with the injection and the oral administration of testosterone propionate in patients with acne. We worked for about three months on a series of about 20 cases. They are not ready to report, and I don't think they will be reported. We have had no success. The patients who were treated by mouth were watched at weekly intervals, and we have seen no improvement from the oral use of this drug, though this is generally considered the most potent form of administration. We have treated a smaller group by intramuscular injections of 25 mg. of testosterone propionate weekly for several months, without any improvement.

Dr. J. Gardner Hopkins, New York: As a clinician who has collected samples of urine but who has not actually made estimations of estrogen, I find it difficult to reconcile the results obtained in different laboratories. Rosenthal and Kurzrok, for example, found an absence of estrogen in many such cases, while Dr. Wile has found a relatively slight diminution and others, I believe, no change. Dr. Wile's studies on androgen break new ground. One must admit that the increases found are small. Whether they are beyond the limits of error of the method I do not know. It is my impression, however, that boys with acne usually show well developed secondary sex characteristics and that one sees severe acne in girls with hypertrichosis and other male characteristics. It does seem that the indications Dr. Wile has found of an increase in androgen seem more in accordance with what is known of acne clinically than a simple decrease in estrogen.

Dr. Udo J. Wile, Ann Arbor, Mich.: Dr. Hopkins has mentioned the diminution of estrogenic substances in acne previously reported by other observers. This was found in our first determinations and was subsequently substantiated by newer methods in our sceond. The results which we have shown from our studies, namely that in the urine of patients with acne of both sexes there are a diminution in the amount of estrogen and a corresponding increase in the amount of androgen, are rather interesting and point not to a specific hormonal dysfunction but rather to a hormonal imbalance as a possible etiologic factor (not necessarily the sole factor) in the causation of acne. Such hormonal imbalance may well be determined by structural changes in the gonadal system and may be definitely associated with the sexual (M/F) ratio of the individual patient. The latter is definitely a developmental matter, and it might be postulated that the determination of whether or not a person is to have acne may be foreshadowed in intrauterine life.

From the practical standpoint one should be guarded in applying these facts to therapeutic procedure. Until more is known about the pathologic physiology of gonadal imbalance it may be dangerous, and at least it is not rational, to inject gonadotropic or estrogenic substances routinely in the treatment of acne. The diminution, for example, of estrogenic output and the increase in androgenic output do not necessarily indicate that these substances are insufficiently produced on the one hand or overproduced on the other. They may indicate improper utilization, resulting in a storing up on the one hand or a too rapid elimination on the other.

However, at present the activity or potency of these substances is subject to considerable variation. When they are extremely potent their empiric use is not entirely free from danger.

In conclusion, therefore, although our studies may eventually have some practical bearing on the treatment of acne, for the present they must be regarded as of more interest from the etiologic standpoint.

LYMPHOGRANULOMA VENEREUM

SERUM LIPIDS AND PROTEINS

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The results of our preliminary study [1] of lymphogranuloma venereum indicated that additional data were necessary. This seemed true especially because in the literature there is little on the biochemical phases of the disease and there appear to be no definite criteria as to cure.[2]

Continued investigation has made possible the accumulation of figures on 150 patients ranging in age from 20 to 57. These have been classified in six groups on the basis of duration of infection, extent of involvement and treatment (table 1). Groups 1, 2 and 3 consist of patients suffering from the inguinal type: 45 untreated in group 1, with involvement of from twelve days' to two years' duration, 23 treated in group 2, affected with the disease for from twelve days to one year, and 9 in group 3 with lesions not more than 6 weeks old; these were examined before and after treatment. Thirty-nine subjects with rectal stricture and esthiomene, mostly of many years' standing, compose group 4. Groups 5 and 6 include patients suffering from both lymphogranuloma venereum and syphilis. For comparison we observed a series of 10 patients with chancroid, comprising group 7, and 33 normal persons, who constitute group 8.

As in our previous communication, the lipid partition—total lipids, total cholesterol, cholesterol esters, free cholesterol and alcohol-ether-

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From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University, Dr. George Miller MacKee, Director.

1. Rosen, I.; Rosenfeld, H., and Krasnow, F.: Lymphogranuloma Venereum; Prolonged Derangement of Serum Lipids and Proteins: A Preliminary Report, Arch. Dermat. & Syph. **36**:318 (Aug.) 1937.

2. Williams, R. D., and Gutman, A. B.: Hyperproteinemia with Reversal of the Albumin: Globulin Ratio in Lymphogranuloma Inguinale, Proc. Soc. Exper. Biol. & Med. **34**:91 (Feb.) 1936. Frei, W.: Venereal Lymphogranuloma, J. A. M. A. **110**:1653 (May 14) 1938.

TABLE 1.—*Summary of Results of Analyses of Serums from Patients with Lymphogranuloma Venereum*

Group	Description of Condition: Type	Description of Condition: Duration	Number of Cases	Total Lipids (Mg. per 100 Cc.)	Cholesterol: Total (Mg. per 100 Cc.)	Cholesterol: Esters: Milligrams	Cholesterol: Esters: Percentage of Total	Cholesterol: Free: Milligrams	Cholesterol: Free: Percentage of Total	Alcohol-Ether Soluble Phosphorus (Mg. per 100 Cc.)	Lecithin (Mg. per 100 Cc.)	Percentage Protein: Albumin	Percentage Protein: Globulin
1*	Fresh, untreated	12 days to 2 years	45	1,421 ±32	176 ±7	101 ±5	56.8 ±1.6	75 ±3	43.2 ±1.6	6.51 ±0.21	162 ±5	4.02 ±0.07	3.53 ±0.10
2*	Treated	12 days to 1 year	23	1,629 ±56	199 ±9	123 ±6	61.0 ±1.7	77 ±4	39.0 ±1.7	7.43 ±0.25	185 ±6	4.21 ±0.07	3.46 ±0.11
3*	Before treatment	12 days to * weeks	9	1,534 ±56	198 ±19	122 ±12	62.0 ±2.5	76 ±8	38.0 ±2.5	6.65 ±0.47	166 ±12	4.17 ±0.18	3.40 ±0.21
	After treatment	12 days to 6 weeks	9	1,686 ±84	216 ±17	127 ±11	58.6 ±1.3	89 ±6	41.4 ±1.3	8.00 ±0.45	200 ±11	4.26 ±0.15	3.55 ±0.25
4	Rectal stricture and esthiomene	6 months to many years	39†	1,426 ±33	176 ±8	102 ±6	57.3 ±1.6	74 ±3	42.7 ±1.6	6.63 ±0.21	165 ±5	3.67 ±0.08	4.24 ±0.15
5	With syphilis—one observation	3 weeks to 11 months	18	1,556 ±53	193 ±12	124 ±10	63.2 ±2.0	70 ±5	36.8 ±2.0	7.56 ±0.31	189 ±8	4.06 ±0.06	3.47 ±0.15
6	With syphilis—repeated observations												
	(*a*) First observation at our clinic	1 month to 9 years	10‡	1,470 ±33	185 ±12	125 ±12	63.2 ±4.7	60 ±4	36.8 ±4.7	7.23 ±0.31	181 ±8	4.13 ±0.10	3.84 ±0.17
	(*b*) Last observation at our clinic	1 month to 9 years	10‡	1,636 ±72	183 ±10	103 ±8	55.9 ±2.7	80 ±4	44.1 ±2.7	7.37 ±0.20	184 ±5	4.00 ±0.12	3.59 ±0.25
7	Chancroid												
	(*a*) With lymphogranuloma venereum	3 weeks to 4 weeks	3	1,499 ±103	197 ±6	125 ±11	63.2 ±3.6	72 ±5	36.8 ±3.6	7.19 ±0.16	179 ±4	4.29 ±0.20	3.32 ±0.22
	(*b*) Without lymphogranuloma	6 weeks to 1 year	7	1,560 ±67	239 ±27	142 ±20	58.4 ±2.7	97 ±9	41.6 ±2.7	7.82 ±0.45	195 ±11	4.38 ±0.21	3.09 ±0.19
	(*c*) Combined series	3 weeks to 1 year	10	1,542 ±55	226 ±18	137 ±14	59.8 ±2.2	90 ±7	40.2 ±2.2	7.63 ±0.33	191 ±8	4.35 ±0.16	3.16 ±0.15
8	Normal		33	1,621 ±32	228 ±6	152 ±4	66.6 ±1.1	76 ±3	33.4 ±1.0	8.02 ±0.13	200 ±3	4.38 ±0.04	2.28 ±0.04

* Inguinal type.
† Except cholesterol (37 cases).
‡ Except total lipids and cholesterol (9 cases).

TABLE 2.—*Distribution of Values for Serum in Lymphogranuloma Venereum with Reference to the Normal Range (Percentage Distribution*

TABLE 2.—*Distribution of Values for Serum in Lymphogranuloma Venereum with Reference to the Normal Range (Percentage Distribution of Values)*

Group	Description of Condition: Type	Description of Condition: Duration	Number of Cases	Total Lipids: Below Normal Average Range	Total Lipids: Within Normal Average Range	Total Lipids: Above Normal Average Range	Cholesterol: Total: Below Normal Average Range	Cholesterol: Total: Within Normal Average Range	Cholesterol: Total: Above Normal Average Range	Cholesterol: Percentage of Esters: Below Normal Average Range	Cholesterol: Percentage of Esters: Within Normal Average Range	Cholesterol: Percentage of Esters: Above Normal Average Range	Cholesterol: Percentage Free: Below Normal Average Range	Cholesterol: Percentage Free: Within Normal Average Range	Cholesterol: Percentage Free: Above Normal Average Range	Alcohol-Ester-Soluble Phosphorus: Below Normal Average Range	Alcohol-Ester-Soluble Phosphorus: Within Normal Average Range	Alcohol-Ester-Soluble Phosphorus: Above Normal Average Range	Percentage Protein: Albumin: Below Normal Average Range	Percentage Protein: Albumin: Within Normal Average Range	Percentage Protein: Albumin: Above Normal Average Range	Percentage Protein: Globulin: Below Normal Average Range	Percentage Protein: Globulin: Within Normal Average Range	Percentage Protein: Globulin: Above Normal Average Range
1*	Fresh, untreated	12 days to 2 years	45	80.0	4.4	15.6	84.4	4.4	11.1	86.7	2.2	11.1	11.1	2.2	86.7	80.0	8.9	11.1	77.8	4.4	17.8	0	2.2	97.8
2*	Treated	12 days to 1 year	23	52.2	8.7	39.1	69.6	8.7	21.7	78.3	0	21.7	21.7	0	78.3	56.5	17.4	26.1	65.2	4.3	30.4	0	0	100.0
3*	Before treatment	12 days to 6 weeks	9	55.6	22.2	22.2	77.8	0	22.2	77.8	0	22.2	22.2	0	77.8	88.9	0	11.1	66.7	0	33.3	0	0	100.0
	After treatment	12 days to 6 weeks	9	33.3	11.1	55.6	55.6	0	44.4	100.0	0	0	0	0	100.0	33.3	22.2	44.4	55.6	0	44.4	0	0	100.0
4	Rectal stricture and esthiomene	6 months to many years	39†	82.1	5.1	12.8	78.4	8.1	13.5	86.5	5.4	8.1	8.1	5.4	86.5	82.1	5.1	12.8	92.3	2.6	5.1	0	0	100.0
5	With syphilis (one observation)	3 weeks to 11 months	18	61.1	0	38.9	83.3	0	16.7	61.1	5.6	33.3	33.3	5.6	61.1	61.1	11.1	27.8	94.4	5.6	0	0	0	100.0
6	With syphilis (repeated observations)																							
	(a) First observation at our clinic	1 month to 9 years	10‡	88.9	11.1	0	88.9	0	11.1	33.3	11.1	55.6	55.6	11.1	33.3	80.0	0	20.0	90.0	0	10.0	0	0	100.0
	(b) Last observation at our clinic	1 month to 9 years	10‡	55.6	0	44.4	88.9	0	11.1	100.0	0	0	0	0	100.0	80.0	10.0	10.0	90.0	0	10.0	0	0	100.0
7	Chancroid																							
	(a) With lymphogranuloma venereum	3 weeks to 4 weeks	3	66.7	0	33.3	0	0	100.0	66.7	0	33.3	33.3	0	66.7	100.0	0	0	66.7	0	33.3	0	0	100.0
	(b) Without lymphogranuloma venereum	6 weeks to 1 year	7	71.4	0	28.6	42.9	0	57.1	85.7	14.3	0	0	14.3	85.7	57.1	0	42.9	57.1	14.3	28.6	0	0	100.0
	(c) Combined series	3 weeks to 1 year	10	70.0	0	30.0	60.0	0	40.0	80.0	10.0	10.0	10.0	10.0	80.0	70.0	0	30.0	60.0	10.0	30.0	0	0	100.0

* Inguinal type.
† Except cholesterol (37 cases).
‡ Except total lipids and cholesterol (9 cases).

soluble phosphorus (lecithin or lipid phosphorus)—as well as the albumin-globulin ratio was determined. Our methods of analysis remained unchanged. The data have been tabulated to show the averages of the respective series with their corresponding standard deviations, $\sigma = \sqrt{\frac{\Sigma d^2}{N\,(N-1)}}$ (table 1 [3]), the percentage distribution of values

TABLE 3.—*Odds Against Random Occurrence of Deviations (Calculations Based on D/P.E.)*

Description of Condition			Number of Cases	Total Lipids (Mg. per 100 Cc.)	Cholesterol			Alcohol-Ether-Soluble Phosphorus (Mg. per 100 Cc.)	Percentage Protein	
					Total (Mg. per 100 Cc.)	Esters (Percentage of Total)	Free (Percentage of Total)			
Group	Type	Duration							Albumin	Globulin
1*	Fresh, untreated....	12 days to 2 years	45	332.40	19,300	1,341	1,341	19,300	415.00	65×10^9
2*	Treated.....	12 days to 1 year	23	.....†	18.82	15.96	15.96	4.64	5.38	65×10^9
3‖	Before treatment....	12 days to 6 weeks	9	1.90	2.57	2.98	2.98	15.96	1.39	1,341
	After treatment.....	12 days to 6 weeks	9	1.00	1.00	655.30	655.30	.....†	1.00	1,341
4	Rectal stricture and esthiomene	6 months to many years	39‡	215.8	1,341	1,025	1,025	19,300	14.7×10^6	65×10^9
5	With syphilis (one observation)	3 weeks to 11 months	18	1.00	9.90	2.21	2.21	1.90	520.40	42.7×10^6
6	With syphilis (repeated observations)									
	(*a*) First observation at our clinic	1 month to 9 years	10§	37.42	37.42	1.00	1.00	8.48	9.90	73×10^7
	(*b*) Last observation at our clinic	1 month to 9 years	10§	.....†	174.90	78.53	78.53	13.58	18.82	1,341
7	Chancroid									
	(*a*) With lymphogranuloma venereum	3 weeks to 4 weeks	3	1.18	116.30	1.00	1.00	142.30	.....	655.3
	(*b*) Without lymphogranuloma venereum	3 weeks to 1 year	7	1.00	.....†	15.96	15.96	.....	.....	267.2
	(*c*) Combined series	3 weeks to 1 year	10	1.63	.....†	13.58	13.58	1.18	.....	19,300

* Inguinal type.
† D/P.E. is less than 0.5
‡ Except cholesterol (37 cases).
§ Except total lipids and cholesterol (9 cases).

with respect to the normal range (table 2) and the odds against random occurrence of deviations from the normal D/P.E.[4]

3. Chaddock, R. E.: Principles and Methods of Statistics, Boston, Houghton Mifflin Company, 1925.

4. Pearl, R.: Introduction to Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1930.

Perusal of these summaries indicates general hyperglobulinemia, which reaches a peak at 4.24 ± 15 mg. per hundred cubic centimeters in lymphogranuloma with rectal stricture and esthiomene (group 4). Even chancroid without lymphogranuloma venereum (group 7) possibly effects an elevation, although to a milder degree. This may perhaps signify an emphasis on the synthesis of globulin which aids the organism in its efforts to detoxify. These findings are convincingly corroborated by the fact that the serum globulin in 100 per cent of cases

TABLE 4.—*Report of Cases*

Designation of Case	Group	Sex	Age	Date	Total Lipids	Cholesterol: Total (Mg. per 100 Cc. Serum)	Cholesterol: Esters (Percentage of Total)	Cholesterol: Free (Percentage of Total)	Alcohol-Ether-Soluble Phosphorus	Percentage Protein: Albumin	Percentage Protein: Globulin	Other Clinical Data
1 B	3	M	28	10/11/37	1,560	207	59.4	40.6	6.15	4.04	3.47	Goose egg-sized tumor somewhat tender in right inguinal region
1 B	3	M	28	1/25/38	1,500	263	62.0	38.0	8.30	4.48	3.60	Received 13 injections of a bismuth preparation
1 A	3	M	26	3/23/37	1,340	139	56.8	43.2	5.30	3.81	3.41	Fluctuating bubo, left side
1 A	3	M	26	4/22/37	1,620	207	58.0	42.0	7.81	3.84	3.29	Received 6 injections of Frei antigen; condition nearly cleared
3 M	4	F	36	5/25/36	1,300	118	55.1	44.9	4.60	3.57	4.43	Rectal stricture, colostomy
4 F	4	F	45	5/11/36	1,400	166	57.9	42.1	7.32	3.95	3.30	Esthiomene

studied was above the normal average range. Furthermore, the odds against randomness of deviations from the normal are high generally (odds above 4 convey probable statistical significance). Thus, any overlapping of normal analytic figures for globulin by those obtaining in lymphogranuloma venereum is definitely obviated. Hyperglobulinemia was found at all times, regardless of the duration of the disease. Few biochemical researches have brought forth such immediate and persistent derangement of any vital mechanism.

The serum lipids, although showing a marked tendency to depletion, were not so drastically disturbed as the proteins. Total lipids, cholesterol and alcohol-ether–soluble phosphorus were decreased. Free cholesterol was increased. It is noteworthy that the few patients with

chancroid uncomplicated by lymphogranuloma venereum whom we examined showed no lowering of the total cholesterol or the alcohol-ether–soluble phosphorus content; hence, the condition may perhaps be distinguished biochemically from lymphogranuloma venereum.

Treatment with intravenous injections of Frei antigen as a rule brought about the return of the total lipid, the cholesterol and the alcohol-ether–soluble phosphorus content to the normal level. The globulin content remained apparently unaffected by such treatment or fluctuated only slightly in cases of early disease, corresponding in obstinacy to the Frei reaction (table 4). Unfortunately, these comparisons have been possible in few cases, so that it is difficult to predict with certainty the degree of success in this direction. Nevertheless, it is of value to have additional objective means for ascertaining how the body is responding.

SUMMARY AND CONCLUSIONS

Further studies of serum in 116 cases of lymphogranuloma venereum corroborated our previous findings.

Hyperglobulinemia in 100 per cent of cases was the most outstanding symptom, being present during all stages and most marked in the late stage (rectal stricture and esthiomene). Hyperglobulinemia may be a valuable diagnostic lead. In cases in which the diagnosis is doubtful and the globulin content high the Frei test should be performed.

The serum lipids (total lipids, total cholesterol and phosphorus) were decreased.

In chancroid there may be an increased globulin content but no decrease in the lipids.

Treatment of lymphogranuloma venereum by intravenous injection of Frei antigen brought the lipid values to normal but left the globulin unchanged.

Dr. Howard Fox, of Bellevue Hospital, and Dr. B. A. Kornblith, of the Department of Health, assisted us in obtaining cases for this study.

TOXIC MANIFESTATIONS IN THE SKIN FOLLOWING SULFANILAMIDE THERAPY

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The administration of sulfanilamide may be accompanied with more or less severe constitutional reactions, such as nausea, lassitude, headache and fever, the last being often confused with the fever produced by the infection. Acidosis, cyanosis or jaundice may occur. The toxic cutaneous manifestations may vary from a maculopapular to a purpuric type of eruption. Cyanosis has been noted in as high as 75 per cent of patients treated with sulfanilamide. Practically every patient receiving sulfanilamide shows a fall in the carbon dioxide–combining power, but clinical acidosis is rare.

Other complications of sulfanilamide therapy include sulfhemoglobinemia, as reported by Discombe.[1] Paton and Eaton [2] have observed sulfhemoglobinemia and methemoglobinemia following the administration of sulfanilamide. A death from agranulocytosis following treatment with sulfanilamide was described by Young [3] and the development of acute hemolytic anemia during sulfanilamide therapy has been reported by Harvey and Janeway.[4]

Sulfanilamide has been used experimentally in a variety of dermatologic conditions with varying clinical results but without a high percentage of cutaneous manifestations of toxicity.

Ingels [5] reported 5 cases of lupus erythematosus in which sulfanilamide therapy was used. In all 5 cases improvement was noted; in

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1. Discombe, G.: Sulphemoglobinemia Following Sulphanilamide Treatment, Lancet **1**:626 (March 13) 1937.

2. Paton, J. P. J., and Eaton, J. C.: Sulphemoglobinemia and Methemoglobinemia Following Administration of *p*-Aminobenzenesulphonamide, Lancet **1**:1159 (May 15) 1937.

3. Young, C. J.: Agranulocytosis and Para Amino Benzene Sulphonamide, Brit. M. J. **2**:105 (July 17) 1937.

4. Harvey, A. M., and Janeway, C. A.: Development of Acute Hemolytic Anemia During Administration of Sulfanilamide (Para-Aminobenzenesulfonamide), J. A. M. A. **109**:12 (July 3) 1937.

5. Ingels, A. E.: Lupus Erythematosus Treated with Sulfanilamide, Arch. Dermat. & Syph. **37**:879 (May) 1938.

2 cases there was complete clearing; in 1 case there was an acute flare-up of the lupus erythematosus, but this subsequently quieted down, and the patient was 50 per cent better than before sulfanilamide was administered. All but 1 of the patients showed a reaction of some type. There were 2 cases of generalized dermatitis medicamentosa.

Menville and Archinard [6] reported a series of 4 of cases of sulfanilamide dermatitis in which there was a definite history of sulfanilamide therapy and exposure to sunlight. It is interesting to note that in these cases the dermatitis appeared to be limited to the parts exposed to the sun. In the first case there was an associated constitutional reaction consisting of chills, fever, pruritus, cyanosis, hyperpnea and nausea. The cutaneous eruption was of the maculopapular type, with the formation of minute unruptured vesicles. This eruption never extended to the remainder of the body and cleared when the drug was discontinued. In the remaining 3 cases also there was a maculopapular type of eruption limited to the parts exposed to sunlight. In none of these cases did the constitutional reaction reach the severity observed in the first case.

Goodman and Levy [7] reported 2 cases of toxicodermatosis following sulfanilamide therapy. In these cases the dermatitis was not confined to exposed areas but was associated with mild constitutional symptoms and signs. In the first case a recurrence of diffuse erythematous blush followed the ingestion of two 5 grain (0.32 Gm.) tablets of sulfanilamide. The cutaneous and intracutaneous tests gave negative results. The condition in the second case was similar to that in the first, except that a possibly positive reaction to a scratch test was obtained. In both cases the eruption cleared satisfactorily after discontinuance of therapy. The authors expressed the belief that the eruption was an allergic one, resulting from induced hypersensitivity to sulfanilamide.

Frank [8] reported 2 cases in which the eruption was more marked on the surfaces exposed to sunlight, but erythema multiforme with an urticarial tendency was present on other parts of the body. He was able to produce a recurrence of the dermatitis by administering sulfanilamide.

A case of generalized purpuric and scarlatiniform eruption developing on the fourth day of treatment was reported by Schonberg.[9] There

6. Menville, J. G., and Archinard, J. J.: Skin Eruptions in Patients Receiving Sulfanilamide, J. A. M. A. **109**:1009 (Sept. 25) 1937.

7. Goodman, M. H., and Levy, C. S.: The Development of a Cutaneous Eruption (Toxicodermatosis), J. A. M. A. **109**:1009 (Sept. 25) 1937.

8. Frank, L. J.: Dermatitis from Sulfanilamide, J. A. M. A. **109**:1011 (Sept. 25) 1937.

9. Schonberg, I. L.: Purpuric and Scarlatiniform Eruption Following Sulfanilamide, J. A. M. A. **109**:1035 (Sept. 25) 1937.

was a preceding eruption of macules and wheals, with severe constitutional symptoms. This eruption cleared in a few weeks, but one month later one 5 grain (0.32 Gm.) tablet produced within four hours a generalized scarlatiniform eruption with associated edema. Schonberg concluded that the patient had a generalized hypersensitivity of the entire organism.

Newman and Sharlit [10] reported 4 cases of sulfanilamide dermatitis in areas exposed to sunlight. They were able to reproduce the dermatitis in previously uninvolved areas by the administration of an erythema dose of ultraviolet radiation. They concluded that sulfanilamide could, by some unknown method, sensitize the skin and that "there may in some measure be a concomitant humoral disturbance able to induce cutaneous changes at a distance."

Salvin [11] reported a case of sulfanilamide dermatitis in which there was a positive reaction to a patch test and in which a small dose of the drug produced a recurrence of the dermatitis. In 3 cases reported by Mainzer [12] there was a recurrence of the rash following resumption of sulfanilamide therapy.

Hageman and Blake [13] reported that a fever and rash occurred in 15 per cent of their cases. They described the lesions as maculopapular, with occasional hemorrhagic and urticaria-like wheals and stated that the usual locations were the buttocks, knees and back, with lesions also occurring on the face, trunk and extremities.

Schwentker and Gelman [14] stated that in 10 per cent of their cases a rash developed, usually appearing without any prodromal symptoms between the third and the fourteenth day of medication. Fever and malaise were always noted and occasionally preceded the eruption by several hours. The blood showed no significant alteration. The rash was distinctly morbilliform and made up of maculopapular reddish brown lesions. Almost the entire body was involved, although occasionally the dermatitis was limited to the buttocks or extremities. The palms and soles were occasionally involved, but the mucous membrane never. The eruption cleared within forty-eight to seventy-two hours after suspension of sulfanilamide therapy.

10. Newman, B. A., and Sharlit, H.: Sulfanilamide: A Photosensitizing Agent of the Skin, J. A. M. A. **109**:1036 (Sept. 25) 1937.

11. Salvin, M.: Hypersensitivity to Sulfanilamide, J. A. M. A. **109**:1038 (Sept. 25) 1937.

12. Mainzer, F. S.: Sulfanilamide Rash, Pennsylvania M. J. **41**:386 (Feb.) 1938.

13. Hageman, P. O., and Blake, F. G.: A Specific Febrile Reaction to Sulfanilamide, J. A. M. A. **109**:642 (Aug. 28) 1937.

14. Schwentker, F. F., and Gelman, S.: Sulfanilamide Rash, Bull. Johns Hopkins Hosp. **61**:136 (Aug.) 1937.

Brunsting [15] has reported several cases of sulfanilamide dermatitis on the parts of the body exposed to sunlight. He was unable to obtain a positive reaction to a scratch test in any case, although he was able to cause a local exacerbation of the dermatitis by exposing an area to ultraviolet rays even though the general eruption was subsiding. In 2 cases an increased amount of porphyrin was found in the urine, 141.5 micrograms as compared with a normal daily excretion of 80 micrograms or less.

Thus it may be seen from the reported cases of sulfanilamide dermatitis that there is no unanimity of opinion as to the cause or the distribution of the dermatitis beyond agreement to the fact that it occurs in patients receiving sulfanilamide or its derivatives. The fact that exposure to sunlight has precipitated many of these dermatoses cannot be doubted; whether this condition would appear later regardless of the exposure cannot be stated. It is logical to assume that any factor which lowers the resistance of the skin beyond a certain point can precipitate the eruption, or, if a sufficient amount of the drug were given, that it would eventually overcome the resistance of the skin and produce more typical toxic dermatoses than those occurring as a result of exposure to sunlight.

Van Studdiford [16] has observed the development of a dermatitis in patients under treatment with sulfanilamide following treatment with hyperpyrexia. In these cases the factor of exposure to sunlight was absent. The precipitating factor was apparently the heat and erythema produced by the fever treatment.

In addition to the well known fact that compounds of the benzene ring have a tendency to produce toxic dermatitis, Frank [8] has brought out the important point that a mild erythema resulting from exposure to sunlight can hasten the appearance of, and for a time localize, many dermatologic conditions. He suggested that heliosensitivity created by the drug or some of the products of its chemical combination with hemoglobin may play a part in this type of toxic eruption.

Fourteen cases of sulfanilamide dermatitis were observed by me during the past fifteen months. In 6 the patient was cooperative enough to permit thorough study and observation. The individual cutaneous lesions due to sulfanilamide were of three general types: First and most frequent were the maculopapular or morbilliform eruptions of rather limited distribution, precipitated or aggravated by exposure to sunlight. It is unknown whether there is a photosensitization of the skin or whether the condition is the result of the irritating effect of the sun's

15. Brunsting, L. A.: Sulfanilamide Dermatitis: Question of Relation to Photosensitivity, Proc. Staff Meet., Mayo Clin. **12**:614 (Sept.) 1937.

16. Van Studdiford, T.: Personal communication to the author.

rays on an already pathologic skin. Second were widely distributed lesions ranging from macules and papules to edema and urticaria-like wheal formations, with occasional coalescence of the individual lesions. This type of dermatitis is probably the most irritating of the three. The patient may be aware of the edema and have associated pruritus. Third and rarest were purpuric eruptions. In 1 case observed such a condition followed prolonged medication, not appearing until the third week. The history did not definitely reveal whether dermatitis had preceded the purpura; examination, however, showed many fine macular lesions associated with multiple purpuric lesions. These were chiefly on the dependent portions of the body, and there was no constitutional evidence of similar lesions of internal organs.

Several cases were observed in which the dermatitis, consisting of a maculopapular eruption with multiple small unruptured vesicles, was limited to the areas exposed to sunlight. This dermatosis responded to elimination of the drug. In 3 cases the patient agreed to resume modified sulfanilamide therapy after ten days. There was no recurrence of the eruption. The patient was advised to avoid exposure to sunlight. After five days in 2 cases suberythema doses of ultraviolet radiation were given to previously uninvolved areas, without recurrence of the dermatitis. In the third case, the same amount of ultraviolet radiation precipitated a generalized eruption. This eruption responded to elimination of the sulfanilamide. A patch test with freshly prepared 1:100 suspension of sulfanilamide gave a negative result. Attempts at passive transfer to persons under sulfanilamide therapy gave negative results, as did attempts at passive transfer to uninvolved parts of the skin of the same person. The level of sulfanilamide in the blood ranged from 104 to 116 mg. per hundred cubic centimeters at the time of the original dermatitis.

These eruptions due to sulfanilamide were all precipitated by exposure to sunlight. In all cases it was possible to resume sulfanilamide therapy. In 2 cases the patient withstood ultraviolet irradiation without recurrence of the dermatitis. In the third a generalized eruption followed ultraviolet irradiation. This occurrence probably indicates that the patient became sensitized to the drug, a fact which places that case among those of toxic dermatosis with sensitization and explains the close relationship between the two types of eruption.

REPORT OF CASES

CASE 1.—Mrs. M., aged 33, was first seen in the clinic with an urticarial type of eruption, of generalized distribution but most marked about the distal portion of the extremities and on the chest and abdomen. She was under treatment with 40 grains (2.59 Gm.) of sulfanilamide daily for cystitis and had been taking the drug for twelve days. Throughout this time she had complained of malaise

and headache. The dermatitis first appeared on the abdomen seven days after the beginning of medication. There were no subjective symptoms until the dermatitis became generalized, after which mild pruritus developed. She had discontinued the medication two days previous to visiting the dermatologic clinic. The individual lesions appeared to be slightly erythematous elevated wheals, and in general the long axes of the wheals followed the lines of cleavage of the skin. In a few areas the individual lesions had coalesced and formed large plaquelike erythematous areas. There were no mucosal lesions and no associated gastrointestinal symptoms. Attempts at passive transfer gave negative results. Blood pressure was 115 systolic and 78 diastolic; the blood picture was normal except for the hemoglobin content, which was 60 per cent; the urine (catheterized specimen) showed a few pus cells, but no abnormal changes in color. The eruption began to fade on the second day of observation, and the patient was given a suberythema dose of ultraviolet radiation, which produced no changes. The dermatitis cleared completely in two weeks. A patch test with 1:100 freshly prepared sulfanilamide gave a negative result. The patient was induced to start sulfanilamide therapy again. After the first dose the dermatitis of the neck and axillas reappeared, and she discontinued the medication. This case was one of apparent sensitization to sulfanilamide resulting in an allergic manifestation of the urticarial type.

Case 2.—Mr. J. H., aged 27, a private patient, complained of an eruption of two days' duration. Examination showed a maculopapular eruption generalized over the entire body. The lesions were most extensive on the face and extremities. He had taken sulfanilamide on his own initiative for the preceding two weeks because of a urethral discharge. After an initial dose of four tablets (20 grains [1.29 Gm.]) every four hours for the first few days he became nauseated and weak and had to remain in bed. He then reduced the dose to two 5 grain (0.32 Gm.) tablets every four hours, which caused no discomfort. The eruption was a vivid red and did not entirely clear on pressure. There were no mucosal lesions, and the urethral discharge had disappeared. The temperature was 99 F., and the blood pressure, 125 systolic and 80 diastolic. The urine showed a trace of albumin but no change in color suggestive of uroporphyrin. The blood showed 68 per cent neutrophils and 80 per cent hemoglobin. A patch test with 1:100 solution of sulfanilamide gave a negative result; the Prausnitz-Küstner phenomenon was absent. The patient was advised to discontinue treatment. This was done, and the dermatitis cleared after seven days. There was mild exfoliation about the wrists and the collar line. The patient began taking the drug again at my request, 40 grains (2.59 Gm.) daily, in divided doses, and at the end of ten days there was no evidence of a return of the dermatitis. He was subjected to a generalized erythema dose of ultraviolet rays, which did not cause the eruption to reappear. Medication was discontinued, and repetition of the ultraviolet irradiation on the fifteenth day produced no results. This case was one of toxic dermatitis due to sulfanilamide in which there was no sensitization to the drug. It was possible for the patient to take sulfanilamide again without the recurrence of a dermatitis.

Case 3.—Mrs. G., aged 49, was referred to the dermatologic clinic because of an eruption on the body. The lesions were maculopapular and purpuric and most prevalent on the lower extremities. Examination of the mucous membrane, eyes, nose, mouth, throat and rectum did not reveal any further lesion. The individual lesions ranged in size from that of a pinpoint to that of a lentil. They did not fade completely on pressure. There was no history of exposure to sunlight. The

Fig. 1.—Sulfanilamide dermatitis, toxic type without sensitization.

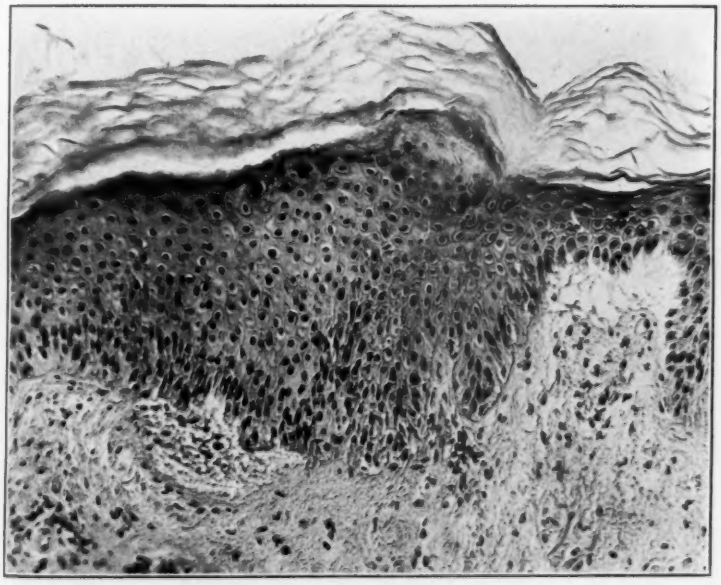

Fig. 2.—Histologic changes in dermatitis precipitated by exposure to sunlight.

temperature was 102 F., the pulse rate 105 and the blood pressure 135 systolic and 90 diastolic. The patient stated that she had had frequent attacks of sore throat, for which she had been directed to take two 5 grain (0.32 Gm.) tablets of sulfanilamide four times daily by her physician three weeks previously. She had continued the medication up to the day she visited the clinic. Urinalysis revealed the presence of severe renal damage and associated oliguria. The sulfanilamide content of the blood was found to be 121 mg. per hundred cubic centimeters. The patient was told to discontinue therapy, and a purge with mild mercurous chloride was given. The dermatitis cleared within two weeks. Patch tests and attempts at passive transfer gave negative results, and the patient was given one 5 grain (0.32 Gm.) tablet of sulfanilamide four times daily. After one week the level of sulfanilamide in the blood reached 110 mg. per hundred cubic centimeters. Ultraviolet irradiation produced no lesions. Therapy was discontinued.

This case was one of toxic dermatitis with purpura in which the system becomes saturated with sulfanilamide owing to improper elimination.

The histologic pictures of the various types of eruption were studied. The toxic dermatoses presented various stages of inflammation and could not be differentiated from sensitization dermatoses. An interesting histologic picture was presented by dermatitis precipitated by exposure to sunlight. The pathologic changes were similar to those of arsenical dermatitis and surprisingly like those of acute lupus erythematosus. These conclusions were confirmed by Michelson.[17]

There were hyperkeratosis, a few subcorneal vesicles and a marked distortion of the basal line, with alteration of the individual basal cells. The granular layer was intact. There was great edema of the tip of the papillae, almost making the vesicle a bulla. In the corium there was a rather limited perivascular infiltration.

CONCLUSIONS

Sulfanilamide therapy may result in several distinct types of toxic dermatosis. The first and most common type is precipitated by exposure to sunlight. In this type the level of sulfanilamide in the blood is not abnormally high, nor is there ordinarily a sensitivity to the drug. However, the combination of factors occurring internally, such as possible abnormal porphyrin metabolism, lowered resistance due to the disease process and the irritative effects of the sun's rays, results in the occurrence of a localized dermatitis which may be complicated by areas of dermatitis at distant points. The second type of eruption is that in which definite sensitivity to the drug occurs, resulting in a sensitization dermatitis. The patient cannot tolerate further sulfanilamide in any dose. The third type of dermatitis is that resulting from poor toleration of, or saturation with, sulfanilamide and presenting the typical picture of toxic dermatosis. The toxic effects of the drug result from

17. Michelson, H. E.: Personal communication to the author.

improper utilization of the drug or from its gradual accumulation in the system. The patient can tolerate further sulfanilamide therapy providing excretory functions are normally resumed and the dosage is properly modified. There is no known sensitivity to the drug in these cases.

ABSTRACT OF DISCUSSION

Dr. Marcus R. Caro, Chicago: Whenever a new drug is introduced that is effective, there is a natural tendency to extend its use in many directions. Sulfanilamide produced such startling results in cases of streptococcic infection that it soon became a popular practice to try it out on all stubborn ailments, especially because of the early belief that the drug was harmless. As reports of its many harmful results were filed, an era of skepticism set in. At present many practitioners are afraid to use the drug, while thoughtful workers are limiting its use to conditions in which its action is apparently specific or in which there is otherwise a hopeless prognosis.

I have used sulfanilamide in many types of cutaneous disorder. I found the greatest incidence of cutaneous reactions in cases of lupus erythematosus, in many of which even small doses of sulfanilamide were followed by a morbilliform eruption. It is significant that a disease which is often aggravated by exposure to sunlight, as is lupus erythematosus, should so often flare up after the use of a drug which itself sensitizes the skin to the sun's rays.

Sulfanilamide tolerance varies greatly. Pediatricians are using the drug freely in the treatment of streptococcic sore throat, otitis media and mastoid infection. I have been told that in contrast to the common experience with adults, toxic reactions in children are uncommon.

The patient with pemphigus vulgaris who was the subject of my recent report (Pemphigus: Treatment with Sulfanilamide; Preliminary Report, Arch. Dermat. & Syph. **37**:196 [Feb.] 1938) has consumed over 5,000 grains (324 Gm.) of sulfanilamide during the past year and is still able to tolerate the drug. On two occasions it was necessary to discontinue therapy because of an attack of urticaria, but both times the treatment was resumed after a short period of rest. By contrast, another patient whom I saw recently had a generalized morbilliform eruption after ingestion of 100 grains (6.5 Gm.) of sulfanilamide in divided doses for postoperative fever. This was soon accompanied with granulocytopenia, and in spite of blood transfusions and the use of pentnucleotide the patient died.

Dr. Tedder has made a thorough study of the toxic effects of sulfanilamide on the skin. His work and similar investigations of its action on other organs are laying the foundation of fact on which it may be possible to build a safe and rational system of indications or contraindications for the use of sulfanilamide.

Dr. Stephan Epstein, Marshfield, Wis.: Dr. Tedder has shown that different types of dermatoses are caused by sulfanilamide. Especially interesting to me were those related to light. Two types of light dermatosis may be distinguished: one demonstrating true photosensitivity, exemplified by hydroa vacciniforme and urticaria photogenica, which is due, one may say, to a specific action of the sun's rays, and one in which radiation is a nonspecific factor, exemplified by erythema mulitforme, lupus erythematosus and drug eruption.

Dr. Tedder put his cases, rightly, among those of the second type, but there is evidence from the literature, especially the reports of L. A. Brunsting, that there also may be true photosensitivity. This seemed rather evident in a case I observed: A boy aged 6 years had urticaria photogenica three weeks after the

discontinuation of sulfanilamide. It was possible within the next ten days to reproduce the eruption by any subsequent exposure to sunlight, even when filtered through window glass.

This experience induced me to carry out a series of experiments (to be published) on the action of ultraviolet rays on sulfanilamide. My results may be summarized as follows:

Two different types of reaction were observed:

1. *A Primary Reaction to Light (Photosensitivity).*—Application at the site of an injection of sulfanilamide of an erythema dose of ultraviolet rays produced plain erythema, about 1 cm. in diameter, which persisted for several days and eventually led to pigmentation. The reaction differed only quantitatively (in intensity and duration) from the erythema of the surrounding skin. The experiment was repeated during the next few days, with the same result.

2. *An Allergic Reaction to Light (Photoallergy).*—Nine days after the first irradiation, a different type of reaction appeared when the site of another injection of sulfanilamide was irradiated. Ten hours after the irradiation an inflammatory reaction with intense itching and swelling appeared, lasting for a week or longer. This reaction was entirely different from the primary one and was produced with every following experiment. It could be elicited only by the action of ultraviolet rays on the injected sulfanilamide. Neither ultraviolet rays without sulfanilamide nor sulfanilamide without radiation elicited this reaction, nor did sulfanilamide irradiated in vitro.

These experiments demonstrate a new type of light reaction, namely a true allergy to light (photoallergy), and may contribute to the understanding of the mechanism of some sulfanilamide dermatoses and possibly of some other diseases in which light is a factor.

Dr. Ben A. Newman, Los Angeles: Before Dr. Sharlit's and my original report on the photosensitizing properties of sulfanilamide (Sulfanilamide: Photosensitizing Agent of Skin, *J. A. M. A.* **109**:1036 [Sept. 25] 1937) appeared in the literature, I had observed about 400 cases of erysipelas treated with this drug. In only 2 cases had any type of toxic dermatitis appeared; and this was a banal type of nondescript toxic erythema. In the spring of 1937, however, after the administration of sulfanilamide to ambulatory patients with nonstreptococcic infection, a special type of dermal response to the drug was seen. This was the photosensitization reaction. The reaction was fairly common, occurring in 8 of 92 cases in which the drug was used. After this observation patients were warned to avoid direct exposure to sunlight, and the incidence of the eruption was greatly reduced.

Dr. Sharlit and I considered two possibilities in the pathogenesis of this photosensitization: (1) that the action of the drug or of part of its molecule was similar to that of the group of photodynamic fluorescent compounds represented by eosin and rose bengal, and (2) that the action was similar to that of the sulfonmethane group of drugs, whose effect on the hematopoietic or reticuloendothelial system is responsible for the production of hematoporphyrin. Examinations of the blood for hematoporphyrin in 1 case gave inconclusive results; hence we attempted the following experiments: 1. Patients having recovered from the photosensitization dermatitis were given intracutaneous injections of a 1 per cent solution of sulfanilamide, and the injected areas were exposed to ultraviolet irradiation and sunlight. No reactions were noted. 2. Daily parenteral administration to guinea pigs of 25 mg. of sulfanilamide per kilogram of body weight, with simultaneous and subsequent exposure to ultraviolet irradiation, produced no reaction.

Since our report C. Rimington (Porphyrinuria Following Sulfanilamide: Sulfanilamide Dermatitis, *Lancet* **1**:770 [April 2] 1938) has reported obtaining a series of porphyrins in the urine of sulfanilamide-treated patients which on occasion contained the coproporphyrins of series I. The latter are highly sensitizing to the skin. I believe these findings to be explanatory of the pathogenesis of the reaction, which is in accord with the sulfonmethane type of intoxication.

I should classify the cutaneous reactions to sulfanilamide as of three types: (1) the banal type of toxic erythema, (2) photosensitization dermatitis, consisting of the dusky red morbilliform maculopapular eruption confined to the sites exposed to sunlight, and (3) a combination of the two.

Dr. James William Tedder, New Orleans: In an effort to determine the value of the patch test, I applied intracutaneous and patch tests to about 100 routine patients in a dermatologic clinic. Less than 2 per cent of these patients gave positive reactions. Two who gave a positive reaction to the patch and the intracutaneous test were placed on sulfanilamide therapy, without the occurrence of dermatitis.

I think Dr. Epstein's case is an example of true sensitivity to light. Cases of this type must be separated from those in which dermatitis is precipitated by exposure to sunlight but in which true sensitivity to light does not exist.

TUMOR-LIKE KERATOSES

REPORT OF A CASE

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SAN ANTONIO, TEXAS

The development of keratoses on the chest of a 27 year old patient after exposures to ultraviolet rays over a period of eighteen months was reported by Colquhoun.[1] Findlay [2] exposed rats to ultraviolet rays and produced keratoses in these animals. He attributed the results to the ultraviolet rays and not to heat, as from an electric bulb. This work was confirmed by Roffo.[3] Findlay stated that in Queensland, Australia, farmers have abandoned the raising of white cattle because of their susceptibility to the development of cancer of the skin.

Roffo [4] reported an increase in the cholesterol content of the skin in exposed areas of the body in contrast to the protected areas. He suggested that these variations in the cholesterol content are referable to heliotropism and expressed the belief that cholesterol is fixed in the skin as a result of its heliotropism. He concluded as a result of his study that cholesterol prepares the soil for subsequent malignant growth by acting as an accumulator of light.

Petersen,[5] in a survey of the distribution of deaths from cancer of the skin, mouth and breast in America, reported a higher death rate from cutaneous cancer in the South among white persons. However, cancer of the mouth and breast had a higher death rate in the Middle West and the East.

Peller and Stephenson [6] reported the incidence of cutaneous cancer in the United States Navy as eight times that in the corresponding civil

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Read before the Section on Dermatology and Syphilology at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 17, 1938.

1. Colquhoun, K. G.: Notes on Cases of Keratoses and Fixed Pigmentary Deposit Following Quartz Light Therapy, Brit. J. Dermat. **39**:346-350 (Aug.-Sept.) 1927.

2. Findlay, G. M.: Cutaneous Papillomata in the Rat Following Exposure to Ultra-Violet Light, Lancet **1**:1229-1231 (June 7) 1930.

3. Roffo, A. H.: Role of Ultra-Violet Rays in the Development of Cancer Provoked by the Sun, Lancet **1**:472-474 (Feb. 29) 1936.

4. Roffo, A. H.: Heliotropism of Cholesterol in Relation to Skin Cancer, Am. J. Cancer **17**:42-57 (Jan.) 1933.

5. Petersen, W. F.: American Distribution of Deaths from Cancer of the Skin, Mouth and Breast, Arch. Dermat. & Syph. **30**:425-432 (Sept.) 1934.

6. Peller, S., and Stephenson, C. S.: Skin Irritation and Cancer in the United States Navy, Am. J. M. Sc. **194**:326-333 (Sept.) 1937.

population. This increased incidence occurs in men exposed to sunshine and salt water. The authors also reported in this group diminished morbidity and mortality rates from all other types of cancer and expressed the belief that exposure to the sun's rays increases the incidence of cutaneous cancer but lowers that of internal cancer.

The southwestern part of Texas receives abundant sunshine. The United States Weather Bureau [7] reported almost twice the amount of sunshine for this region as for the Middle West and the East. This probably accounts for the lowered incidence of psoriasis in the Southwest. However, the devastating cutaneous effects of exposure constitute a real hazard of living. This is probably explained by the popularity of sun tan, sun baths and nudism, together with the fact that an abundant amount of sunshine is available throughout the year.

Smith [8] called attention to chronic actinic dermatitis as an occupational hazard of the Southwest. He pointed out that keratoses develop in young persons. The outdoor life of the patients predisposes them early to cutaneous changes usually not encountered until after the fourth decade of life. It is not uncommon to see from five to twenty keratoses and several carcinomas in the same young person. Obviously these changes develop much earlier and to a more exaggerated degree in the blond or red-haired freckle-faced type than in the brunet.

Native races in geographic areas receiving an abundant amount of sunlight have acquired a pigmentary protection to this hazard of living. However, migration of races has transplanted persons with light-sensitive skins into an environment totally unsuited for them. Cutaneous changes resulting from exposure to the elements in elderly persons are considered as an expected senile change. The skin is dry and scaling and presents pigmentary disturbances. The hands and face also present atrophy, telangiectasia, keratoses and in many instances carcinomas. The general picture is that of actinic dermatitis. In numerous instances one of the earliest cutaneous manifestations of exposure is the development of multiple spider nevi. This occurs chiefly in persons who move into the Southwest from other parts of the country.

The cutaneous manifestations of acute actinic dermatitis may vary greatly in different persons. The usual picture when the involvement is severe is one of intense erythema, edema, vesicles and bullae. This usually subsides in from four to seven days, resulting in exfoliation and hyperpigmentation. Examples of acute actinic dermatitis usually follow exposure in persons whose occupation keeps them indoors. I shall report an unusual and unique sequela of acute actinic dermatitis in a lawyer:

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7. United States Weather Bureau: Personal communication to the author.

8. Smith, L. M.: Chronic Actinic Dermatitis: An Occupational Hazard of the Southwest, Texas State J. Med. **33**:644-647 (Jan.) 1938.

REPORT OF CASE

Mr. J. S. McC., aged 45, was seen on Oct. 16, 1937, complaining chiefly of tumors of the skin. Two and a half months previously he had gone fishing in the Gulf of Mexico near Corpus Christi, Texas. He had spent two entire days in the surf, and his hands had been severely sunburned. It required about ten days for the erythema and edema to subside. Shortly after this he noticed small growths appearing over the dorsum of the left hand and one single lesion on the dorsum of the right hand. He had had two similar experiences, when single tumors developed on his hands after a blistering sunburn, incurred as a result of an entire day spent fishing in the gulf. It required seven or eight months for the tumors to reach the height of their growth and then undergo spontaneous involution. When questioned he stated that he had seen examples of such "barnacles" on fishermen along the coast, invariably resulting from severe sunburn.

Examination showed him to be well developed and nourished, with cutaneous tumors over the dorsum of both hands. A single cherry-sized tumor was present

Fig. 1.—Tumor-like keratoses.

on the right and six tumors on the left hand. The single tumor on the right hand was round and firm, with a definite translucency or pearly appearance. The lesions appeared to be carcinoma clinically. On the left hand three of the tumors were large, the largest measuring 2 cm. in length, 1.5 cm. in width and 1 cm. in height, and three smaller, measuring 0.5 cm. in height. These were clinically carcinomas. They were round, firm and translucent.

In addition to these tumors there were many flat warts over the hands. A biopsy specimen was taken from the smallest tumor. The pathologists reported squamous cell carcinoma, grade 1.

The patient returned to the hospital on Nov. 2, 1937, at which time the single large tumor on the right hand was excised. Half of this tumor was ground up in glycerin and passed through a Berkefeld filter. The other half was used for culture material and additional microscopic sections. It was noted at this visit that some of the tumors were undergoing involution, while several were still enlarging. Tissue was sent to Dr. Fred Weidman, in Philadelphia. Microscopic sections were also sent to Dr. Hamilton Montgomery and to Dr. Udo J. Wile. Their opinions will be given later.

The patient was seen later, and all the lesions had completely involuted. No treatment was ever instituted.

COMMENT

Numerous articles[9] dealing with seborrheic and senile keratoses (verruca senilis and keratoma senile) have appeared in the literature. The chief points of differentiation will be briefly discussed. The occurrence of the tumors on the dorsum of the hand with no lesions elsewhere in the case reported was unusual. Stryker[10] stated that seborrheic keratoses do not occur on the dorsum of the hand, while Eller[9a] stated that he had never seen the lesions in this location. However, location of the lesions would not in itself establish the differential diagnosis.

Another differentiation is in appearance. Seborrheic keratoses are usually pigmented flat-topped oval lesions presenting a greasy scale. The lesions usually occur on the face, chest and back and do not appear suddenly or involute spontaneously. Furthermore, seborrheic keratoses have been classified as nevi (delayed) by Darier[11] and others.[12]

The clinical course is rather definite, in that the lesions gradually increase in number over a period of years and no reference has been made to factors of stimulation.

The following report is that of Montgomery,[13] of Rochester, Minn.:

I have carefully studied all the sections you sent me from the patient who had severe sunburn of the hands following a fishing expedition on the Gulf Coast. The histologic picture is that of exuberant verruca vulgaris, if I may be permitted to use such an adjective. The histologic picture closely simulates that of condyloma acuminatum. It is well known that lesions of condyloma acuminatum in the past have been erroneously diagnosed as squamous cell epithelioma.

The regular pattern of acanthosis and relatively few mitotic figures, the invasion of the epidermis by the infiltrate in the cutis, the marked papillomatosis

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9. (*a*) Eller, J. J., and Ryan, V. J.: Senile Keratoses and Seborrheic Keratoses, Arch. Dermat. & Syph. **22**:1043-1060 (Dec.) 1930. (*b*) Hookey, J. A.: Keratoma Senilis and Verruca Senilis, ibid. **23**:946-959 (May) 1931. (*c*) Montgomery, H., and Dörffel, J.: Verruca senilis und Keratoma senile, Arch. f. Dermat. u. Syph. **166**:286-296 (Sept.) 1932. (*d*) Montgomery, H.: Verruca Senilis and Keratoma Senile, Minnesota Med. **18**:735-738 (Nov.) 1935. (*e*) Freudenthal, W.: Verruca senilis und Keratoma senile, Arch. f. Dermat. u. Syph. **152**:505-528, 1926.

10. Stryker, G. V.: Keratoses of the Face and Hands: Differential Diagnosis Between Precancerous and Benign Keratoses, J. Missouri M. A. **30**:15-17 (Jan.) 1933.

11. Darier, J.: Verruca planes senilés, in Précis de dermatologie, ed. 4, Paris, Masson & Cie, 1928, p. 263.

12. Dawson, J. W.: Melanomata, Their Morphology and Histogenesis: A Study of Cell Origins and Transformations with a Critical Discussion on Aspects of Tumour Growth and Clinical Review, Edinburgh M. J. **32**:501-732 (Oct.) 1925. Hookey.[9b]

13. Montgomery, H.: Personal communication to the author.

and engorgement of the capillaries and papillary bodies and the peculiar pattern of the parakeratotic cells in the stratum corneum all speak for verruca vulgaris and against a malignant change.

At first glance, one would naturally think of squamous cell epithelioma of a low grade 1. I have seen more marked epithelial proliferation and regular pearl formation in other cases of pseudoepithelial hyperplasia, including bromoderma, blastomycosis and the edges of the ulcers of noduloulcerative syphiloderm.

The clinical picture in this case was not that of verruca vulgaris. The only point of similarity was the spontaneous involution. As previously mentioned, these tumors were not verruca clinically but were smooth and had the appearance of cutaneous carcinoma. The process of involution was also different from that seen in verruca vulgaris, in that in these tumors a hard keratotic mass replaced the central portion and as this

Fig. 2.—Low power magnification, showing circumscribed character of the lesion and its constituent lobules of epithelial cells. No strands of infiltrating cells can be seen. A mass of keratinous material is apparent in the center of the lesion, near the surface.

gradually increased in size an umbilicated lesion was formed. Throughout the entire course of observation no similarity to verruca was noted.

Sections were also sent to Drs. Wile [14] and Belote [15] at Ann Arbor, Mich.

Dr. Wile's letter in part follows:

Opinion here differs on the microscopic appearance. Dr. R. C. Wanstrom, of the pathologic department, and Dr. G. H. Belote both believe that this is a cornifying squamous cell epithelioma. I do not share this opinion. In spite of the presence of a large number of epithelial whirls, to me the picture is one of dyskeratosis and marked hyperkeratosis.

14. Wile, U. J.: Personal communication to the author.
15. Belote, G. H.: Personal communication to the author.

With Belote and Wanstrom agreeing with Todd [16] in the diagnosis of carcinoma and in the face of continued enlargement of the tumors at this particular time, it was difficult to resist institution of treatment.

Dr. Weidman's [17] report from Philadelphia is given in full:

Following a fishing trip on the Gulf of Mexico, a severe sunburn of the hands developed, with edema. Ten days was necessary for recovery. Thereafter six tumors developed on the back of the left hand and one on the right. In addition, there were many flat warts. As shown in Dr. Poth's photograph, the tumors are 6 to 15 mm. in diameter, highly elevated above the skin, dome shaped and covered by fairly thick scale. There is not any surrounding infiltration.

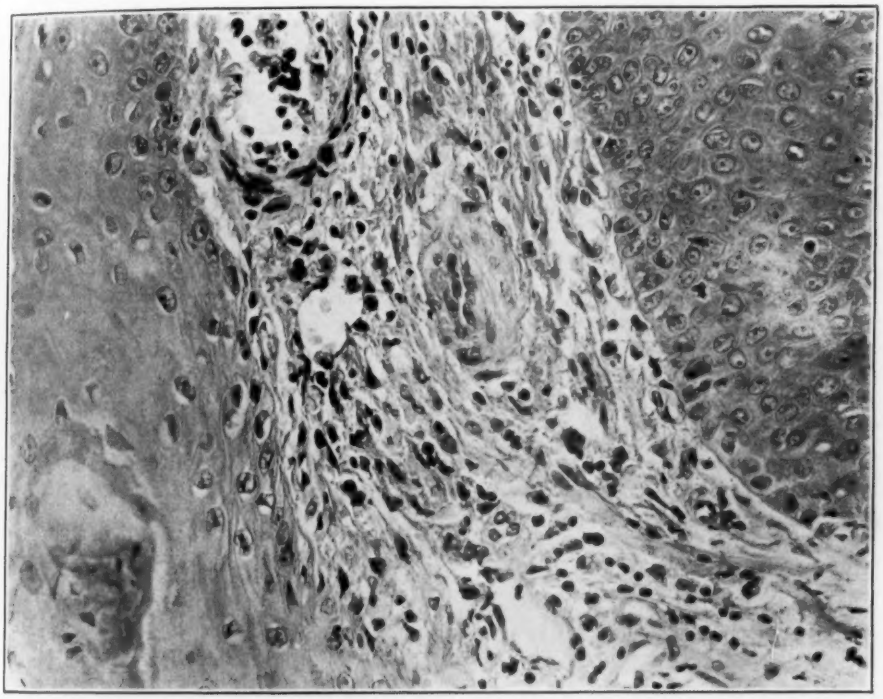

Fig. 3.—High power magnification of a section from the deepest and most active part of the lesion. Neither the gross architecture nor the finer cytologic features are those of cancer.

Similar tumors have followed previous sunburn during fishing in salt water, taking about six months to undergo involution. The present lesions are regressing without treatment.

MICROSCOPIC DESCRIPTION

About 75 per cent of the lesion was removed for microscopic study, and the rest was left in place; that is, the plane of surgical excision passed through the lower portion of a large, more or less spherical mass. The surface of the skin was

16. Todd, D. A.: Personal communication to the author.
17. Weidman, F.: Personal communication to the author.

not ulcerated, and nowhere in the section was there any evidence of suppuration. There was a thin stratum of dense hyperkeratotic material on the surface. At the center of the section this was continued downward, "invaginated," and accumulated in the center of the section to produce a mass of pearly bodies. The latter numbered scores and ranged from small ones to extremely large ones. Surrounding the mass there was a lining of markedly thickened epiderm arranged on fibrous projections of stroma after the fashion of verruca vulgaris, the tips of the villosities being directed toward the interior of the keratinous mass. This architecture was much better seen under the loupe than under the microscope. In short, the histologic picture was that of verruca vulgaris whose summit had been forcibly invaginated to a notable distance and around which the retained keratinous materials had accumulated as though in a cyst.

Both over the surface of the skin and over the villosities the prickle cell layer was enormously hyperplastic. However, in neither position did the cells exhibit a degree of activity suggesting carcinoma. The stratum granulosum was broad and conspicuous, and the prickle cells themselves were large, exhibited their spines exquisitely and extended almost to the basement membrane. That is, the basal cells were not at all hyperplastic. In keeping with this, there was no evidence of permeation of the basement membrane.

The stroma of this epithelial mass was extremely scanty; when present it was rather richly infiltrated with lymphocytes and a few plasma cells. It was not particularly vascular.

As indicated previously, the lowermost parts of the lesion were not submitted for study; hence the question of cancerous change with permeation of tissue cannot be answered for those parts.

COMMENT

The promptly developing cancer-like nodules were apparently due to actinic rays. The history of previous attacks in which the lesions spontaneously disappeared recalls the habits of tar cancer. The histologic picture was akin to that of senile keratosis on an exaggerated scale; here again the factor of actinic rays obtained.

In my opinion, the lesion was not malignant except in the sense that senile keratosis is. My diagnosis was tumor-like senile keratosis.

EXPERIMENTAL WORK

Half of one tumor was ground up in glycerin and passed through a Berkefeld filter. The filtrate was injected into 4 white rats, 2 of which were given excessive doses of radiation from the quartz mercury vapor glow lamp at the site of injection. The remaining 2 were subjected to intradermal injections. Two rats used as controls did not receive injections. No cutaneous change was noted as late as six months after injection.

The filtrate was also injected into two sites on the left and two on the right hand of the patient. Normal skin was used on both hands, and in addition the filtrate was injected into a wart on each hand. The sites of injection on the right hand were then exposed to several erythema doses of radiation from the quartz mercury vapor glow lamp, while those on the left hand were not irradiated. No cutaneous change was noted as long as six months after the injections.

This work was done in order to rule out the possibility of a virus tumor. It was thought in the beginning that some change might have taken place in the verrucae present on the patient's hand as a result of the severe actinic dermatitis. However, no tumors resulted from injections of the glycerin filtrate, either in the patient or in the white rats. The filtrate was used three days after preparation, and 0.2 cc. was injected intradermally in all instances.

As the patient had had two similar experiences, blistering doses of ultraviolet radiation were not given in an attempt to reproduce the tumors. Five tumors still remained on his hand at the time this work was carried out.

All cultures and smears were negative.

SUMMARY

A report is made of the development of tumors varying in size from that of a bean to that of a cherry on the dorsum of the hands after severe sunburn of the hands during a fishing trip in the Gulf of Mexico. The patient's hands were erythematous and exfoliating for about ten days. When seen two and one half months later, the tumors were in every respect identical in clinical appearance to cutaneous epithelioma. Biopsy at this time was reported by Todd [16] as showing squamous cell carcinoma. Material was obtained for further microscopic sections, as well as for experimental work. The opinions of Drs. Montgomery, Wile, Belote, Wanstrom, Todd and Weidman have been presented. Their opinions varied. Verruca vulgaris, carcinoma and tumor-like keratosis were diagnoses obtained from them.

Experimental work consisted of injection of a glycerin filtrate made from one of the tumors. It is felt that the negative results obtained ruled out the possibility of virus tumor.

All the tumors involuted spontaneously within eight months after onset. No treatment was ever instituted.

It was felt that a diagnosis of tumor-like keratosis resulting from cellular stimulation following a severe sunburn was justified in the face of the evidence presented.

Two previous cases of lesions of identical onset and appearance are recalled. However, the tumors were single growths. In both cases the lesion was treated as epithelioma, and microscopic sections were not made. Definite proof as to the exact cellular structure is therefore lacking. In both cases a rapidly growing tumor promptly followed severe actinic dermatitis.

CONCLUSIONS

A unique case of tumor-like keratoses developing on the dorsum of the hands after severe sunburn is reported.

The tumors presented a striking clinical and pathologic resemblance to cutaneous epithelioma.

The tumors underwent spontaneous involution.

It is suggested that other similar lesions might have been diagnosed and treated as epithelioma.

Dr. Henry Leopold permitted me to study the patient.

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ABSTRACT OF DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: The members should be grateful to Dr. Poth for his presentation of this unusual case. If Dr. Poth is correct in his observations, we may be witnessing today the first presentation of a new, unusual cutaneous condition. However, Dr. Poth is not at all dogmatic in his diagnosis of "tumor-like keratoses," but has pointed out that other physicians have felt that the lesions were warts or epitheliomas. In favor of their being epitheliomas was the clinical appearance and the opinion of a competent pathologist. The multiplicity of the lesions and their spontaneous disappearance were not in keeping with the usual concept of epithelioma, but they are features that are rarely seen. In the *Annales de dermatologie et de syphiligraphie* (**7**:545 [June] 1936) A. Touraine and Duperrat presented a résumé of cases of spontaneously disappearing epitheliomas. Also, J. F. Smith and J. S. Dunn in the *British Journal of Dermatology and Syphilis* (**46**:519 [Dec.] 1934) published an article dealing with the same subject.

There is considerable evidence in favor of the idea that the lesions are variants, or certain aberrant types, of common warts. In the first place, as Dr. Poth pointed out in his paper and showed on the screen, there were several common warts—small, it is true—on the dorsum of the hands around these lesions. Second, the hand with the warts was exposed to intense stimulation by sunlight; it is possible that the sunlight might have been the factor causing proliferation of the smaller warty tumors. Third, their spontaneous disappearance might have been similar to that of multiple warts when one of their number is removed by excision—analogous to Dr. Poth's removal of a specimen for biopsy. Next, this spontaneous disappearance might possibly have been introduced, or influenced by, his injection of the filtrate of one of the lesions—analogous to Biberstein's treatment of warts with a filtrate.

On first thought it would seem that the experimental inoculation would have proved that the lesions could not be warts, because no tumors developed at the site of inoculation; but in a publication of mine several years ago (ARCH. DERMAT. & SYPH. **32**:102 [July] 1935) I showed patients in whom warts developed at the site of inoculation of filtrate from warts eighteen months afterward. In other words, possibly the time which has gone by in Dr. Poth's case is not sufficient to prove that these inoculations will not later "take."

DR. R. H. CROCKETT, San Antonio, Texas: Dr. Poth showed me his patient. The lesions had the appearance of rapidly growing tumors, but were more piled up and less scaly than the average keratosis. I have observed 2 cases of lesions which I now think were similar to those in Dr. Poth's case. In each case there was one tumor about the size of a dollar on the back of the hand. The outside was markedly piled up. In the center there was marked evidence of involuting tissue. Sections showed grade 1 squamous cell carcinoma. Treatment was instituted in both cases and recovery followed. I believe if the lesions had not been treated they would have entirely involuted.

I had another case of a lesion resembling that in Dr. Poth's case to some extent. The patient was a man aged 70, with widespread heavy keratotic tumors on his face—the upper lip in particular. Clinically several of them had become malignant. The patient became insane and was sent to an asylum where he stayed in the shade for two years. I happened to see him in the corridor one day, and his entire face was as smooth as though he had never had a keratosis. I think that proves that exposure to sunlight has a great deal to do with the causation and the continuation of these keratoses.

I believe the lesions in Dr. Poth's case were definite rapidly growing keratoses and that either the keratotic tumors were unusual or the patient's reaction to them was unusual. It is possible that these tumors in another person would have gone on to definite malignant change, while this patient by the reaction of his cells was able to throw off the tumors when the causative stimulation of the sun's rays was withdrawn, just as my patient did after two years of freedom from exposure to sunshine.

Dr. C. F. Lehmann, San Antonio, Texas: It is not uncommon, in what is called the keratosis season, which starts about the middle of June and lasts well into October, to see many keratoses in persons whose occupation keeps them outdoors. It has never been my experience to see anything like what Dr. Poth reports, but it is not uncommon to see inflammatory keratoses. My criterion in treating them has always been the matter of time—their duration. It is not uncommon for ranchers to present keratoses with markedly indurated bases, and if they have existed only a month or two I give them time before treatment. A usual observation is their flattening after they are protected from bruises, infections and sunlight. Certainly not without this concept could the lesions in Dr Poth's case fit into the group of purely inflammatory keratoses.

Another point about this case is the very interesting speculation: Does the condition represent a form of mutation from keratosis into epithelioma? That would bring up the question of whether epithelioma is cancerous from the beginning and not precancerous. I shall profit from this paper by being stimulated to do more biopsies in cases of inflammatory keratosis.

Dr. Merlin Trevor-Roper Maynard, San Jose, Calif.: I should like to ask two questions. Was there any history of ingestion of bromine or of arsenic? And did the warts on the fingers disappear when the other lesions disappeared?

Dr. James H. Mitchell, Chicago: The case has been so excellently presented that I hesitate to bring up a question. The ingestion of bromide is so common and it is so difficult to get a history of it that I should like to ask what attempt was made to exclude ingestion of such drugs.

Dr. Fred D. Weidman, Philadelphia: In the final analysis, the general matter of chronic (idiopathic?) epithelial hyperplasia is under discussion. There are many stages, from verruca vulgaris to carcinoma. Certainly all of the stages have not yet been catalogued exhaustively. They may have been catalogued more or less from the histologic angle; they have been catalogued perhaps less precisely from the clinical angle, but after that there still remains the problem of cataloguing them after reconciling these two angles—that is, of analyzing and classifying the different combinations of changes clinically and histologically. What Dr. Poth has done for dermatology is to add one more item to the list of different combinations of dyskeratotic change that constitute a clinical entity.

Of such clinical entities there are already verruca vulgaris, the plantar wart, molluscum contagiosum, senile keratosis, tar cancer and finally outright prickle cell cancer. This list constitutes an ascending scale of combinations of clinical

circumstances and histologic changes. If an attempt is made to fit the condition that has been described by Dr. Poth into that scale, I should say that it stands somewhere between senile keratosis and tar cancer. The histologic changes were those of a 4 plus senile keratosis, but that in association with the clinical considerations does not justify classifying the condition as outright senile keratosis. On the other hand, it can scarcely be called tar cancer, because there has been no tar factor clinically. Of course it was not cancer, because (in my opinion) the histologic picture was not that of cancer and of course the clinical course shows that it was not cancer.

I am inclined to agree heartily with Dr. Poth that this is a new entity, something that we easterners have learned to expect when we come to some other part of the country. From what is known of the role of actinic rays in senile keratosis, it is not surprising that both the clinical and the histologic picture of that disease should appear here.

I might say that the histologic picture in this case was not that of a halogen dermatitis; there was not the edema, the extreme infiltration or the vascularity seen in such a disease.

Dr. W. F. Spiller, Galveston, Texas: I was interested in Dr. Poth's case because he mentioned that the man had been fishing in the gulf. Many keratoses occur in that region, especially in fishermen, and Dr. Poth's statement interested me, because a large majority of these keratoses are of the type that he described and occur often in persons who have been fishing. I was wondering if the combination of salt water and sunshine had something to do with the cause of this condition.

In cases I have observed biopsy is usually reported as showing low grade squamous epithelioma. I have considered the disease a fisherman's or sailor's disease because it occurs more often in fishermen and sailors than in other persons.

Dr. Duncan O. Poth, San Antonio, Texas: In answer to Dr. Templeton, there was no resemblance at all to xeroderma.

Dr. Templeton reports the spontaneous disappearance of true cancer. To my knowledge, this has never been reported as occurring on the dorsum of the hand—that is, squamous cell epithelioma of the dorsum of the hand, to my knowledge, has never been reported as undergoing spontaneous involution. Spontaneous involution of carcinoma elsewhere has been reported.

The infiltrate was injected into this patient after microscopic proof of involution was seen, so that the question of treatment with an infiltrate does not seem to be important to me. The flat warts are still present on the patient's hands.

In answer to Drs. Maynard and Mitchell, this patient entered the hospital in December 1936, with miliary pulmonary tuberculosis. He was hospitalized from December until the latter part of May. During that period none of the halogens was administered. The exposure occurred at the time of his first outing after hospitalization, which probably accounts to some extent for the severity of the sunburn in this particular instance. I did not examine his urine or blood for halogens, because they had never been administered.

The patient told me that he had seen the condition among fishermen along the gulf coast. I was interested to hear Dr. Spiller report such a case.

I spent a great deal of time trying to find instances of similar disease or some one who had seen the lesions develop in fishermen, because if such a thing happens, there must be some factor in addition to exposure to the sun's rays.

XANTHELASMA AND LEPROSY

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SAM H. BLACK, M.D.

AND

HILARY ROSS, B.S.

NEW ORLEANS

For many years xanthelasma has been observed among the inmates of the United States Marine Hospital (National Leprosarium) at Carville, La., but the frequency of its occurrence was not disclosed until a survey was made in the early part of 1937. In this survey xanthelasma was found in 27 of 243 lepers examined. For comparison, the orbital regions of 235 tuberculous patients in the wards of the Charity Hospital in New Orleans were examined by Dr. J. B. Colligan. In this group 144 patients were over 30 years of age and 77 were over 40. Xanthelasma was not found in any of the 235 tuberculous patients. Dr. Alfred Gage made a similar examination of 200 patients at the clinic of Tulane University of Louisiana, including all applicants for admission. In this group 37 patients were over 30 years of age, and 48 were over 40. Xanthelasma was found in 2 persons.

DISTRIBUTION OF LESIONS

In leprosy of the cutaneous type the lesions on the upper eyelids show a predilection for the ciliary border. The region of the eyelid above the ciliary border usually is free of lesions, even in advanced nodular disease. Small lepromas may cover almost all of the ciliary border, causing loss of cilia, but extension upward occurs slowly, and even in disease of many years' duration the central area of the lid usually remains conspicuously normal. In exceptional cases in which lepromas appear in the central area of the lid, their occurrence is the result of peripheral extension of lesions situated below or above this region.

On the lower lid leprous lesions are frequently found on the ciliary border, with resulting loss of cilia.

In xanthelasma on the upper eyelid of lepers, no predilection for the ciliary border was noted. On the contrary, the border was free even

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in cases of extensive lesions. In a few instances oval plaques of xanthelasma with their long axes in the horizontal plane extended almost to the border of the lid, but in no case did the plaques cover the border of the lid, nor did loss of cilia occur as a result of xanthelasma. A few of these plaques (as Wile noted) were lower on the lid than would be expected in typical xanthelasma, but not as low as would be expected in leprosy. Single plaques of xanthelasma

Fig. 1.—Leprous lesions in the supraorbital region and on the ciliary border of the upper eyelids. In *A* the visible area appears equally involved, and loss of cilia is apparent. *B* shows the same patient, with the eyes closed. There are no lesions in the area between the supraorbital region and the ciliary border.

were frequently seen in the central part of the lid in cases in which the orbital region elsewhere appeared normal.

Xanthelasma was not found on the ciliary border of the lower lid.

In leprosy, regions exposed to trauma, such as the extensor surfaces of the elbows and knees, are sites of predilection for nodular lesions; the distribution of leprous lesions in this respect is similar to that of xanthoma tuberosum, except that leprous lesions do not occur in scar

tissue. In xanthelasma and in leprous lesions of the orbital region, however, our survey disclosed a difference in distribution, which would not be expected if trauma were an important factor in determining the sites of xanthelasma, as it is in determining those of leprosy.

We have believed that the ciliary border of the upper lid is more exposed than the central area above it to irritation from wind, light and temperature, because that part of the lid above the ciliary border is covered by a fold of skin, under which it is protected when the eyes are

Fig. 2.—Xanthelasma and leprosy on the upper eyelids. *A* shows involvement of the ciliary border with leprous lesions and xanthelasmic lesions almost hidden by folds of skin. *B* shows the same patient, with the eyes closed. The xanthelasmic lesions are plainly in view.

open. It is when the eyes are open during the waking hours that exposure to such irritants naturally occurs, for when the eyes are closed in sleep and the area above the ciliary border is not covered, the environment of the person is such that irritation from these natural agents does not occur. The upper eyelid, we therefore believe, is not an exception to the general rule that regions of the cutaneous surface most exposed to trauma are sites of predilection for leproma.

If trauma were a factor in determining the sites for development of xanthelasma on the upper eyelid, as it is of leprosy and of xanthoma tuberosum in other regions, it is difficult to understand why the exposed ciliary border of the upper eyelid was not involved in our cases of xanthelasma while in the central protected area above the ciliary border xanthelasmic plaques frequently occurred. As evidence of the difference in the distribution of the lesions on the upper eyelids in leprosy and xanthelasma, and as evidence that exposure is a factor in this distribution

Fig. 3.—Scars on the buttocks, surrounded but not invaded by infiltrated leprous patches.

in the former and not in the latter, may be mentioned the fact that observation of the lids when the eyes are open shows leprous lesions, especially those on the ciliary border, to be plainly in view, while plaques of xanthelasma, if they happen to occur in the central area of the lid, are hidden by a fold of skin.

CONFIGURATION AND COLOR

The xanthelasmic plaques were more distinctly marginated than were the nodules of leprosy. When the skin was stretched the yellow color

of the plaques showed to advantage in contrast with the normal skin, and the sharpness of the line of demarcation between the plaques and the normal skin was even more apparent. Xanthelasmic plaques, although elevated above the surrounding normal skin, were usually not rounded, as were the nodules of leprous lesions.

In both diseases the longer diameter of oval patches was most often in the horizontal plane. In only a few cases of xanthelasma did the reverse proportion obtain. In leprosy exceptions to the rule were even less frequent.

The usual red, brown or purplish color of lepromas does not in the least resemble the yellow of xanthelasma, and the yellowish brown color due to deposition of pigment in some leprous macules in regions other than the orbital differs considerably from the yellow of xanthelasma, in which there is no admixture of brown.

It may be of interest to note that in addition to the 27 lepers in whom xanthelasmic plaques occurred, 16 were seen in whom, although there were no plaques, the orbital region was discolored with a yellowish tinge, extending in some cases over the whole area. In these cases the yellow was that of xanthelasma. In several other cases a similar condition was observed on the neck; in 2 instances yellow nodules occurred on the arms, and in 1 a leprous infiltrated patch on the forehead was distinctly yellow in the center while the periphery of the patch was the color usual in leprosy. In all these cases the extraorbital yellow nodules were few in comparison with the coexisting lepromas of the usual leprous color.

BACTERIOLOGIC AND HISTOLOGIC STUDY

Eleven biopsy specimens of xanthelasmic plaques from areas usually immune to leprosy in the orbital regions of 6 patients were studied.

The epidermis showed little or no change, except that as a rule it was thin and occasionally a few cells in the basal layer showed vacuolation in the cytoplasm. Directly beneath the epidermis a thin layer of connective tissue of normal appearance was usually present. In the corium all the lesions showed greatly varying numbers of mononuclear cells with markedly vacuolated cytoplasm and characteristic of foam cells. These cells were characteristically distributed in perivascular clumps of varying sizes. In many clumps several capillaries were seen. As a rule these clumps were surrounded by bands of connective tissue varying greatly in width. Leukocytic infiltration was confined almost exclusively to lymphocytes, and this was never diffuse. The foam cells were large, the average varying between 25 and 40 microns in diameter. The membrane of these cells stood out with exceptional clearness. The nuclei, averaging 7 or 8 microns in diameter, were round or oval and as a rule stained deeply with hematoxylin. The cytoplasm was charac-

teristic of foam cells showing vacuolation of the cytoplasm, which in most instances left only a lacy reticulum that stained with the paraffin technic of embedding. In each instance the foam cells when cut by

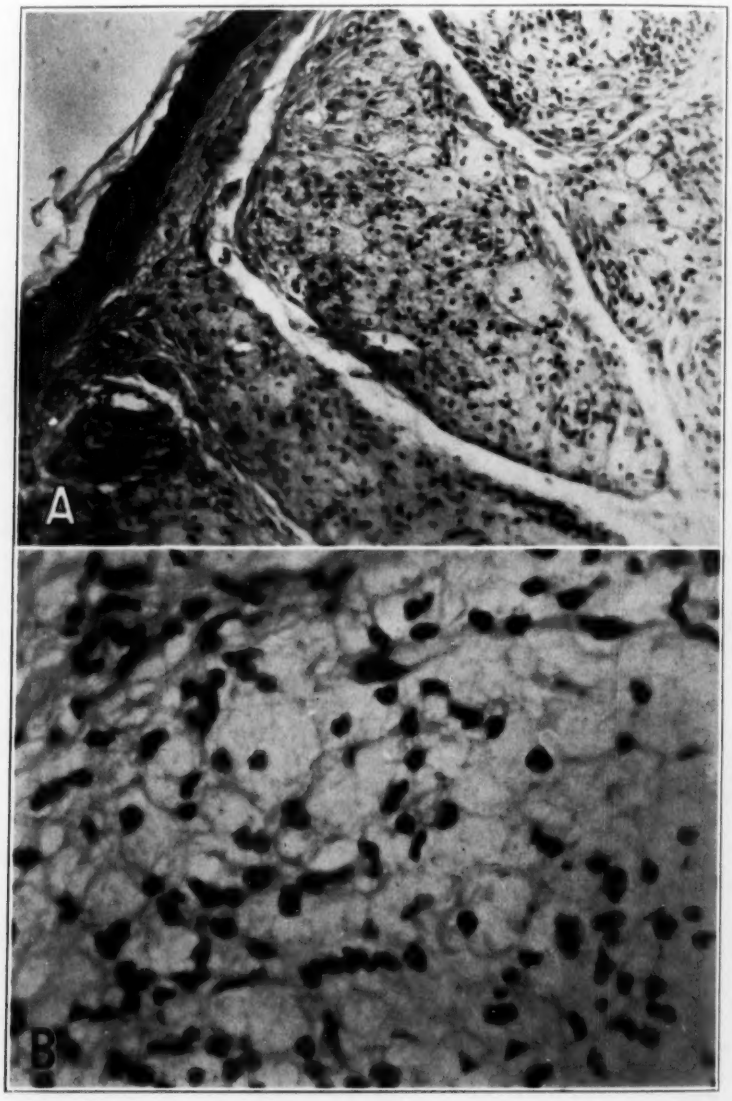

Fig. 4.—*A*, photomicrograph showing characteristic histologic changes of one of the xanthelasmic lesions. Hematoxylin and eosin; × 140. *B*, photomicrograph of the same area, showing foam cells. Hematoxylin and eosin; × 600.

freezing and stained with sudan III showed diffuse collections of fat representing the vacuolated areas of the cytoplasm.

Frozen sections stained by the Ziehl-Neelsen method failed in all but 1 instance to show acid-fast bacilli in the cells; in that instance a few scattered acid-fast bacilli were seen. Sections stained by Van Gieson's method did not seem to implicate the muscle fibers as a source of origin for fat cells. A point that seems worthy of mention is the similarity in the histologic picture of xanthoma and of leproma. Both are composed chiefly of foam cells; appropriate stains show the cytoplasm of one to contain fatty substances, and that of the other, acid-fast bacilli. Both appear to be of perivascular origin. The epidermis is thin in both lesions, and the papillary layer is usually obliterated. The leprous cell as a rule is smaller and more diffusely distributed throughout a well developed lesion. The membrane of the xanthoma cell is more clearly outlined. The leprous cells do not tend to accumulate in groups surrounded by connective tissue as do the xanthoma cells.

In 14 cases of xanthelasma in which biopsy was not done, scrapings of the lesions were examined for acid-fast bacilli. Acid-fast bacilli were present in scrapings in 10 cases. The higher percentage of lesions showing acid-fast bacilli by the scraping than by the histologic method is in agreement with our previous experience that acid-fast bacilli occurring in small numbers are more easily demonstrated in smears made of scrapings than in tissue obtained for biopsy.

In biopsy specimens of yellow lesions taken from the arms in 2 cases previously mentioned it was not possible with hematoxylin and eosin to separate the xanthomatous from the purely leprous part. However, with sudan III the xanthomatous portion was clearly outlined. The fat-laden cells were grouped into areas which macroscopically showed yellow discoloration but were not seen in other portions of the lesions. Acid-fast bacilli were present throughout the lesions, but were not nearly so numerous in the area of the xanthoma cells as in the lesions elsewhere. What happens in such a lesion is not clear; however, as the lesions were subsiding, it seemed reasonable to suppose that decomposition of acid-fast bacilli was taking place. This brings up the question of whether the formation of xanthoma cells in these instances was the result of changes in situ or of a general disturbance of the metabolism of fats.

Plewes [1] concluded that the foam cells of xanthoma arise from the reticuloendothelial system and that the lipoid substances in these cells are not the product of a degenerative process but have been phagocytosed by the cells. It is believed that this study emphasizes Plewes's view and further shows the similarity of the foam cells of xanthoma to the foam cells of leproma. Undoubtedly the foam cell of leproma arises by phagocytosis of Mycobacterium leprae, the body of which is clearly

1. Plewes, L. W.: Nature and Origin of the Xanthoma Cell, Arch. Path. **17**:177 (Feb.) 1934.

demonstrable in the cytoplasm; and certainly the so-called leprous cell is characteristic of the phagocytes commonly regarded as arising from the reticuloendothelial system.

Dr. Hamilton Montgomery examined necropsy tissue from 1 patient and slides of biopsy material from 4 xanthelasmic lesions. He stated that there "seemed to be a typical histopathologic picture of xanthelasma of the eyelids." One additional slide presented an atypical picture.

In lepers acid-fast bacilli are often found in skin which appears normal, and their presence in a lesion does not necessarily imply that the lesion is of leprous origin. In lepers acid-fast bacilli have been found even in nevi and in carcinomas. It is therefore not unreasonable to infer that in xanthelasma seen in lepers the bacilli of Hansen occasionally observed in the sites of the lesions are not the direct cause of the xanthelasmic plaques. This view harmonizes with that expressed by Montgomery and Osterberg [2] in reference to the origin of hyperlipemia and hypercholesteremia in xanthoma tuberosum. However, the fat believed to be present as an envelope surrounding each Hansen bacillus is suggestive of a correlation between the bacilli and the increased lipoid content of the blood serum. In a majority of cases xanthelasma occurred in leprosy of the cutaneous type and in an advanced and active stage. In other words, xanthelasma occurred most often in those cases in which bacilli were most numerous and active and in which toxic effects on the blood might more reasonably be expected than in cases of neural or incipient disease, in which the bacilli are comparatively few. Although in the cases in which xanthelasma was found there may have been gross disfigurement from leprous lesions, the persons were usually robust and not lacking in adipose tissue.

BIOCHEMICAL ANALYSIS

Studies of the total lipoids of the blood, of fatty acids, of lecithin, of phosphatide, of total and free cholesterol and of cholesterol esters were made in 21 cases of xanthelasma. For comparison, the same studies were made in 41 cases of leprosy in which xanthelasma was not found. As a control, the blood of 10 presumably normal persons, employees of this institution, was used. Urinalysis was made in all cases. Determinations of blood sugar were made in all the 21 cases of xanthelasma.

Approximately 15 cc. of blood was collected from a cubital vein after a twelve hour fast. Plasma was used for the determinations of total lipoids and fatty acids, and whole blood, oxalated, for the studies of lecithin, cholesterol, cholesterol esters and sugar. The total lipoids

2. Montgomery, H., and Osterberg, A. E.: Xanthomatosis: Correlation of Clinical, Histopathologic and Chemical Studies of Cutaneous Xanthoma, Arch. Dermat. & Syph. **37**:373 (March) 1938.

were determined by the method of Bloor [3]; the fatty acids by the method of Bloor, Pelkan and Allen [4]; the lecithin by the method of Harnes [5]; with Leiboff's [6] apparatus for the extraction fitted with a condenser, as improvised by Harnes; the total cholesterol according to the method of Bloor [7] and the cholesterol esters by the method of Bloor and Knudson [8]; for both, the Liebermann-Burchard reaction as modified by Mirsky and Bruger [9] was employed to determine the color development, and the free cholesterol by subtracting the chloesterol esters from the total cholesterol.

In all studies identical methods and reagents procured in one lot and prepared at the same time were used. The determinations were all made within one or two months.

In the control group the average findings for the total lipoids, fatty acids, lecithin and phosphatides were comparable with those of Peters and Van Slyke.[10] The average findings for total and free cholesterol and cholesterol esters agreed with the previous findings of two of us.[11]

In the group of lepers in whom xanthelasma was not found the average findings for the total lipoids and the fatty acids fell within the normal range. The average values for lecithin were considerably lower. The total cholesterol, as well as the esters, averaged higher. Of the 41 cases, hyperlipemia was noted in 1. The lecithin content was normal in 1 case and below normal in 40. Twenty-seven patients showed normal values for total cholesterol, while 14 showed definite hypercholesteremia. Of the 27 showing a normal value for total cholesterol, 13 showed a definite increase in the percentage of esters, while of the 14 cases of hypercholesteremia, an increase was found in 8. The urinalyses showed no albumin or sugar in any case.

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3. Bloor, W. R.: A Method for the Determination of Fat in Small Amounts of Blood, J. Biol. Chem. **17**:377, 1914.

4. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, J. Biol. Chem. **52**: 191, 1922.

5. Harnes, A. R.: The Colorimetric Determination of Lipoid Phosphorus in Blood, J. Biol. Chem. **77**:405, 1928.

6. Leiboff, S. L.: A Simplified Method for Cholesterol Determination in Blood, J. Biol. Chem. **61**:177, 1924.

7. Bloor, W. R.: The Determination of Cholesterol in Blood, J. Biol. Chem. **24**:227, 1916.

8. Bloor, W. R., and Knudson, A.: Precipitation of Free Cholesterol and the Determination of Cholesterol Esters, J. Biol. Chem. **27**:107, 1916.

9. Mirsky, A., and Bruger, M.: A Note on the Liebermann-Burchard Color Reaction for Cholesterol, J. Lab. & Clin. Med. **18**:304, 1932.

10. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1.

11. Black, S. H., and Ross, H.: Blood Cholesterol in Leprosy: A Study of the Total and Free Cholesterol, Cholesterol Esters, Van den Bergh Reaction, and the Complement Fixation Test, Pub. Health Rep. **50**:50, 1935.

In the group of lepers in whom xanthelasma was found, the average findings for total lipoids and fatty acids approximated those of the controls. The average value for lecithin approximated that in the group in which xanthelasma was not present. The total amount of cholesterol, as well as of esters, averaged higher than for lepers in whom xanthelasma was not found. Of the 21 cases, hyperlipemia was noted in 1 and a low value for lecithin in 19. In 7 there was a normal value for total cholesterol and in 14 definite hypercholesteremia. Of the 7 cases of normal total cholesterol, the percentage of esters was above normal in 6, while of the 14 cases of hypercholesteremia, the percentage of esters was increased in 10. The value for blood sugar was within the normal range in all cases. Urinalyses showed no albumin or sugar.

Biochemical Analysis of Three Groups

	Mg. per 100 Cc. of Plasma		Mg. per 100 Cc. of Whole Blood					
					Cholesterol			
	Total Lipoids	Fatty Acids	Lecithin	Phospha-tide	Total	Free	Esters	Esters, %
Controls								
Minimum	375	235	205	8.2	120	40	79	47
Average	490	324	232	9.3	168	68	100	59
Maximum	600	408	255	10.2	192	89	143	72
Lepers Without Xanthelasma								
Minimum	416	216	142	5.5	133	22	62	42
Average	586	382	163	6.5	223	66	128	66
Maximum	938	629	203	8.1	240	120	188	87
Lepers With Xanthelasma								
Minimum	441	192	150	6.0	181	11	142	60
Average	632	388	163	6.8	233	51	179	78
Maximum	1071	798	237	9.5	302	107	230	94

A tabulation of the minimum, average and maximum findings in the 21 cases of xanthelasma in association with arrested, improving, stationary or retrogressing leprosy shows that the values for total lipoids and fatty acids varied among the groups into which the cases have been divided, although they fell within the normal range. The average findings for total and for free cholesterol were lowest in cases of retrogression, and the average results for esters were highest in this group.

Division of the group in which xanthelasma was found according to the type of leprosy, for comparison of the lipoid content of the blood in neural and in cutaneous leprosy, was not of much value, because the number of cases of purely neural disease was not sufficient to permit conclusions. The few cases in which xanthelasma occurred in the purely

neural type, however, suggest reference to an observation of Weidman and Schaffer [12] who stated in a summary:

> Attention is directed to the sheaths of cutaneous nerves as a possible source of cutaneous xanthoma cells and the possibility is suggested that the process is analogous to the histogenesis of the notorious neurofibroma of the auditory nerve. Such a theory would reconcile xanthomas of the acoustic nerve with those of the skin.

Such a theory would also "reconcile" neural with cutaneous leprosy.

In a recent article Schaaf [13] reported a series of experiments on animals in support of the view that loss of a particular function of the liver (regulation of the concentration of fat-emulsifying agents in the blood) may result in "an impairment of the colloid dispersion of fats in the blood serum, which increases the tendency of the fats to be thrown out of emulsion." He stated that the development of xanthoma may follow the disturbance of the existing ratio between the important emulsifying agents.

Schaaf's explanation, that the loss of a particular hepatic function is the cause of the altered lipoid contents of the blood, does not as aptly apply in the case of the leprous as it does in that of the nonleprous, for the reason that the alteration in the blood of lepers might be caused by leprosy in many ways other than by its action on the liver. Nevertheless, the view that hepatic dysfunction might be an important etiologic factor in the xanthelasma of lepers is interesting, for could it be established, it might be extended to explain certain phenomena of leprosy for which an adequate explanation is now lacking. Schaaf presented evidence to show that this dysfunction is subject to variations in degree, and these variances, with resulting changes in the lipoid contents of the blood, might explain the frequent appearance and disappearance in leprosy of those acute inflammatory reactions of cutaneous and neural symptoms which apparently are not accompanied with increased proliferation of bacilli of Hansen. Disease of the liver is common in leprosy. In reports of autopsy on 96 lepers at the National Leprosarium, disease of the liver was noted in almost all cases. These figures may or may not be significant, because there is no evidence that the pathologic changes of the liver observed post mortem impaired during life that particular function of the liver which controlled the ratio of the fat-emulsifying agents in the blood serum. Nor is there evidence that the pathologic changes were not such as could be expected in diseases similar to leprosy. Indeed, the histopathologic picture of the liver, which was studied in all cases in which autopsy was performed, showed in most instances leprous involvement due to direct infection of the liver

12. Weidman, F. D., and Schaffer, H. W.: Xanthoma of the Skin and Larynx, Arch. Dermat. & Syph. **35**:767 (May) 1937.

13. Schaaf, F.: On the Experimental Production of Xanthomas in Laboratory Animals, J. Invest. Dermat. **1**:11, 1938.

with Hansen bacilli. The lipoid contents of the blood are being further studied in connection with diet and the acute symptoms of leprosy. Black and Ross [11] have reported on the Wassermann reaction and the cholesterol content of the blood in leprosy but have found no definite correlation. Further observations are being made.

AGE

It was not possible to determine from the histories of the patients whether xanthelasmic patches antedated the development of leprosy. In most cases, however, xanthelasma occurred at or after middle age, while leprosy in most cases occurred before that period.

In no lepers under 30 years of age was xanthelasma found, although 23.8 per cent of the lepers included in the survey were less than 30 years old. Although these figures do not disclose whether leprosy antedated xanthelasma in any individual case, they do indicate that the usual sequence was for leprosy to develop before—in some instances many years bofore—the development of xanthelasma. If this inference is correct, leprosy, the altered ratio of fat-emulsifying agents in the blood serum and the presumptive loss of a particular function of the liver cannot explain the occurrence of xanthelasma in lepers without the assumption of another, as yet undetermined factor, which becomes active only after the onset of middle age.

It is tentatively submitted that factors due to characteristics of the skin of the orbital region result in a local unbalanced ratio of the fat-emulsifying agents in the blood serum. Edema (often designated as "puffiness of the eyelids") is not infrequent in the loose tissue of the orbital region and perhaps results in a dilution of the serum sufficient to disturb fat metabolism. It may be true that the eyelid, because of its thinness, is easily affected by osmosis of tears through the mucous membrane of its under surface. Dilution of the plasma may occur to a greater extent in the loose tissue of that part of the eyelid in which xanthelasma is found than in the firmer tissue of the ciliary border. It is perhaps significant that xanthelasma occurs at an age at which the skin of the orbital region often becomes edematous. It may be significant also that in 5 of the 32 cases of xanthoma of the eyelids alone reported by Montgomery and Osterberg there was serious disease of the cardiovascular system.[14]

SEX

Of the total of 243 lepers examined in this survey, 171 were male and 72 female. Of the 171 males, xanthelasma was found in 20, approximately 11.7 per cent. Of the 72 females, xanthelasma was found

14. Montgomery and Osterberg,[2] p. 394.

in 7, approximately 9.7 per cent. From these almost equal percentages, it may be inferred that sex is not an important factor in the development of xanthelasma in lepers, although sex is of great importance in the origin of leprosy.

In almost all countries in which statistics on leprosy have been recorded, the incidence in men is twice or more as great is in women. McCoy [15] and Hasseltine have presented data from Hawaii and the United States, respectively, in a small number of cases of leprosy on the incidence according to sex in young children. Of 15 children under 5 years of age, 6 were boys and 9 were girls. In the succeeding decade the incidence increased rapidly in both sexes, but more rapidly in boys than in girls. Lowe [16] stated in a summary that the disproportionate incidence is "less marked in childhood than in adult life." No adequate explanation for the etiologic importance of sex has been offered. Speculation, however, in regard to the possibility that dysfunction of the pituitary gland causes the altered lipoid contents of the blood of lepers is interesting, because it suggests an approach to the problem of the disproportionate incidence of leprosy in men and in women. It has been observed that in nonleprous persons there are a difference in the lecithin content of the blood of men and of women and a difference in the sedimentation time. Castration has been said to alter the lipoid contents of the blood of men and menstruation to affect that of women.

SUMMARY

In a survey of 243 lepers in the National Leprosarium, xanthelasma was found in 27, approximately 11 per cent. We inferred from this incidence a correlation between leprosy and xanthelasma.

The lipoid contents of the blood of lepers varied from normal, the greatest variation occurring in the content of cholesterol esters, which occurred to a greater extent in the group of lepers in whom xanthelasma was found.

The greatest variation from normal in the lipoid contents of the blood of lepers was found in active, advanced cutaneous leprosy; xanthelasma was also more frequent in leprosy of this kind than it was in incipient and neural leprosy.

It is probable that changes in the ratio of fat-emulsifying agents in the serum resulting from leprosy are etiologic factors in the xanthelasma of lepers.

This altered ratio may be due to disease of the liver of leprous origin, causing loss of that particular function which controls the ratio.

15. McCoy, G. W.: A Statistical Study of Leprosy in Hawaii, Public Health Bulletin 66, United States Public Health Service, 1914, p. 21.

16. Lowe, J.: The Sex Incidence of Leprosy, Internat. J. Leprosy **2**:71 (Jan.-March) 1934.

Autopsy of 96 lepers has disclosed disease of the liver in almost all cases, but no evidence has been obtained of the existence during life of a dysfunction of the liver which might influence fat metabolism, nor have symptoms of disease of the liver been frequent in lepers.

It is inferred from the distribution of the lesions that trauma in the orbital region is not an important factor in determining the sites for plaques of xanthelasma, but is important in that for leprous lesions.

The age of the lepers in whom xanthelasma was found was in no instance less than 30 years and in the majority of instances was more than 40 years. It is inferred that age is an important factor in the xanthelasma of lepers and that leprosy occurs as a rule prior to xanthelasma. In many cases leprosy was acquired in early youth, and lipoid changes in the blood presumably had existed for many years; yet xanthelasma did not develop until changes in tissue due to advancing years occurred in the orbital regions.

It is tentatively suggested that certain characteristics of the skin of the orbital region at the advent of middle age predispose to edema and that dilution of serum resulting from edema is a contributing factor in the deposition of fat in the xanthelasmic lesions.

As far as the cause of leprosy is concerned, the importance of the altered lipoid contents of the blood of lepers depends on whether these changes occurred prior or subsequent to the development of leprosy. For obvious reasons, data to establish the sequence have not been obtained.

CUTANEOUS REACTION

WITH REFERENCE TO THE SURFACE p_H, THE REACTION TO OINTMENTS AND SOLUTIONS OF DIFFERENT p_H AND THE EFFECT OF THE SKIN IN MODIFYING THE p_H OF APPLIED SOLUTIONS

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The hydrogen ion concentration of the skin has been the subject of a number of studies in recent years. On the basis of regional and pathologic variations in the acidity of the cutaneous surface, certain hypotheses concerning the physiologic significance of these have been developed, and attempts to treat certain dermatoses by changing the surface acidity have been made.

In the present study, in which a simple and rather different method has been used, we have attempted (1) to obtain further data concerning the variation in the hydrogen ion concentration of the surface of the skin, (2) to determine accurately the effect of the skin on the p_H of acid and alkaline solutions coming in contact with it, (3) to determine the threshold of irritability of normal and scarified skin, so far as the hydrogen ion concentration of the contact substance is concerned, and (4) to check the clinical validity of the hypotheses concerning the relation of the alkalinity of the cutaneous surface to certain dermatoses. From our preliminary experiments it was evident that the standard patch test has serious shortcomings in maintaining the concentration of aqueous test solutions, and these will be discussed.

The available data concerning the hydrogen ion concentration of the skin may be summarized briefly: Normal intact skin tends to have a lower p_H at the surface and in the basal layers of the epidermis than

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From the Departments of Dermatology and Syphilology, John H. Stokes, M.D., Director; and of Physiological Chemistry, D. Wright Wilson, Ph.D., Director, University of Pennsylvania.

in the deeper portions of the cutis.[1] The surface of the skin tends to be more alkaline in those portions in which the evaporation of sweat is retarded.[2] Determinations of the p_H of the surface of pathologic skin show variable values, in general higher than those of normal skin.[3]

Burckhardt [4] has tested the response of the skin of normal and eczematous patients to solutions of calcium hydroxide applied in patch tests. He reports that while only 20 per cent of persons with normal skin reacted to 10 or 15 per cent aqueous suspensions of calcium hydroxide, 90 per cent of patients with eczema reacted. The eczematous patients were found to be sensitive to various substances, and Burckhardt concluded that alkaline noxious agents damage the skin, especially of those who are sensitive to alkali. He expressed the belief that the damaged skin is more easily sensitized to a variety of substances, with a consequent susceptibility to eczema. Burckhardt [5] has also tested the neutralizing power of the skin on pieces of filter paper moistened with a drop of 1:2,000 sodium hydroxide and of phenolphthalein solution. The filter paper is covered with a glass block, and the time required to decolorize the phenolphthalein is determined repeatedly. He found that the neutralizing function of the skin is less rapid in alkali-sensitive patients and in aged persons and that it is not due to sweat, to sebum or to the thickness of the keratin layer.

Various methods have been used in determining the acidity of the skin. These have included the application of indicators to the surface of the skin and their introduction into various portions of it. Levin and Silvers [3b] have used the quinhydrone electrode on the surface of the skin, and Schade and Marchionini [6] have employed a glass electrode

1. Unna, P. G., and Golodetz, L.: Zur Chemie der Haut: Hautreagenzien, Monatsh. f. prakt. Dermat. **50**:451, 1910. Comel, M.: Fisiologia normale e patologica della cute umana, Milan, Fratelli Treves, 1933, vol. 1, p. 473. Sharlit, H., and Scheer, M.: The Hydrogen-Ion Concentration of the Surface of Healthy Intact Skin, Arch. Dermat. & Syph. **7**:592 (May) 1923.

2. (*a*) Levin, O. L., and Silvers, S. H.: The Possible Explanation for the Localization of Ringworm Infection Between the Toes, Arch. Dermat. & Syph. **26**:466 (Sept.) 1932. (*b*) Marchionini, A.: Untersuchungen über die Wasserstoffionenkonzentration der Haut, Arch. f. Dermat. u. Syph. **158**:290, 1929.

3. (*a*) Perutz, A., and Lustig, B.: Ueber die Wasserstoffionenkonzentration der Hautoberfläche und ihre Regulation bei Dermatosen, Arch. f. Dermat. u. Syph. **163**:18, 1931. (*b*) Levin, O. L., and Silvers, S. H.: The Reaction of the Skin and Its Secretions in Eczema, Arch. Dermat. & Syph. **25**:825 (May) 1932. (*c*) Scholtz, W.: Ueber säure Behandlung von Hautkrankheiten, Klin. Wchnschr. **9**:1670, 1930.

4. Burckhardt, W.: Die Rolle des Alkali in der Pathogenese des Ekzems speziell des Gewerbeekzems, Arch. f. Dermat. u. Syph. **173**:155, 1935.

5. Burckhardt, W.: Die Rolle der Alkalischädigung der Haut bei der experimentellen Sensibilisierung gegen Nickel, Arch. f. Dermat. u. Syph. **173**:262, 1935.

6. Schade, H., and Marchionini, A.: Zur physikalischen Chemie der Hautoberfläche, Arch. f. Dermat. u. Syph. **154**:690, 1928.

which could be introduced to various levels. Rothman [7] has well summarized the advantages and disadvantages of various methods, and in particular he has emphasized the difficulty of determining the p_H of tissue by direct contact with indicators.

Initially we attempted to determine the surface p_H of the skin and its reaction to buffer solutions of various p_H by patch tests. Pieces of filter paper of standard size were saturated with distilled water or the same amount of various buffer solutions and applied for varying periods. The resulting p_H was determined either by application of an indicator solution to the paper or by immersion of the paper in a small amount of water, with the addition of the indicator. Extremely variable results were obtained. It was found that these were not due to variations in the filter paper or to changes in the final dilution of the indicator. When indicators were applied directly to the paper itself, matching of colors was difficult, and variations in the same square of paper were noted.

It seemed probable that in tests applied for several hours appreciable changes in the concentration of the salts in the buffer solutions had occurred. Accordingly, experiments were performed to determine the loss of fluid from saturated gauze applied to the skin in the usual fashion as a patch test, pieces of cellophane and adhesive tape of adequate size being used as the occlusive agents. After the fluid remaining on the skin when the gauze was taken off immediately was allowed for, variable losses were found, but in general they were under 5 per cent during the first hour, between 50 and 60 per cent in twenty-four hours and over 70 per cent in forty-eight hours. From these experiments it was obvious that such wide variations occurred in the amount of fluid retained in patch tests applied to the skin for twenty-four hours that any interpretation of the final hydrogen ion concentration was impossible.

We have therefore used a method of applying solutions to the skin by which they are completely occluded from the air.

METHOD

The test solutions were applied by means of glass cups 1 cm. in diameter and 0.7 cm. in depth (internal dimensions), the edges of which were rounded to avoid cutting into the skin. They were inverted on the skin and kept in place by adhesive strips. On the extremities it was possible to keep them in contact for forty-eight hours without any loss of the contained fluid. Only moderate pressure from the tape was necessary (fig. 1). The skin was not specially prepared before the cups were applied.

7. Rothman, S.: Die aktuelle Reaktion der Haut (H- und OH-), in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, vol. 1, p. 325.

The test solutions consisted of Sørensen's standard buffer mixtures, Walpole's acetate solutions, Palitzsch's borate solutions and Clark and Lubs' standard mixtures. Solutions were prepared at intervals of p_H 0.2 ranging from p_H 1.04 to p_H 2 and from p_H 4.4 to p_H 12.9. These solutions have been described by Clark.[8] The precautions in the preparation of solutions and in their preservation suggested by Clark [8] were observed.

The indicators employed were thymol blue, bromphenol blue, bromcresol green, chlorphenol red, bromcresol purple, bromthymol blue, phenol red, metacresol purple, tolyl red and parazo orange. With these indicators determinations on clear colorless solutions within an error of p_H 0.1 were possible from the acid side to p_H 9.6. Less accurate determinations were possible in the ranges from 10.8 to 11.4 and from 12 to 12.6.

The acidity of the cutaneous surface was determined by placing approximately 0.4 cc. of distilled water in one of the glass cups, inverting it on the

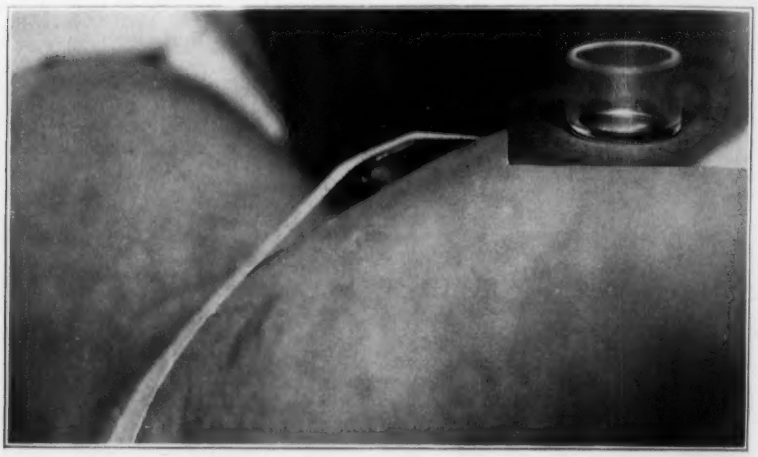

Fig. 1.—Glass cup attached to the arm by a band of adhesive tape. The level of fluid can be discerned inside the cup. The insert shows a close view of the glass cup used in these experiments.

surface of the skin, allowing it to remain in contact for thirty minutes and determining the p_H of the contents. In determining the effect of the skin on buffer solutions of varying p_H, exactly 0.3 cc. of the solution was placed in the cup and allowed to remain in contact with the skin for varying periods up to twenty-four hours.

EXPERIMENTAL RESULTS

Hydrogen Ion Concentration of Cutaneous Surface in Various Portions of Body.—The hydrogen ion concentration of distilled water of an initial p_H of 5.9 applied to several portions of the cutaneous surface in closed cups for thirty minutes was determined for 20 subjects. The areas tested were the flexor surface of the finger, the flexor surface of

8. Clark, W. M.: The Determination of Hydrogen Ions, Baltimore, Williams & Wilkins Company, 1928, p. 192.

the forearm, the extensor surface of the forearm, the axilla, the groin and the fourth interdigital space of the foot. The determinations in the axilla and the groin were made in the extreme lower portion because of the discomfort incident to application of adhesive tape on hairy sites. In most of the experiments duplicate determinations were made on corresponding sites of each side of the body; the difference in p_H of the two sides was never over 0.2.

From the results listed in table 1 it may be seen that the p_H of the cutaneous surface of similar portions of the body varies in different persons. This variation may be as high as 2. The average values for the extensor and the flexor surfaces of the forearms were lowest, being p_H 5.3 and 5.1 respectively. The flexor surface of the index finger had a higher value, an average of 5.4. The axilla and the groin were more alkaline, with readings of p_H 5.8 and 5.7. The fourth interdigital space

TABLE 1.—*Hydrogen Ion Concentration of Cutaneous Surface of Various Portions of Body of 20 Patients (Normal Skin)*

Area	Highest Individual p_H	Lowest Individual p_H	Average
Flexor surface of index finger	6.3	4.7	5.4
Flexor surface of forearm	6.9	4.5	5.1
Extensor surface of forearm	6.8	4.2	5.3
Axilla	7.0	4.6	5.8
Groin	6.1	5.0	5.7
Fourth interdigital space of foot	7.7	5.7	6.5

of the foot gave the highest average p_H value, 6.5. Notes were made on each subject concerning excessive sweating, seborrheic oiliness of the skin, ichthyosis and maceration between the toes. No correlation between any of these factors, with the exception of maceration, and the p_H of the cutaneous surface was noted. When that factor was present, the surface was always more alkaline.

Response of Normal and Abraded Skin to Extremes of Acidity and Alkalinity.—The response of normal skin to buffer solutions of different p_H from 1.2 to 12.6 was determined for 12 subjects. The response of abraded skin was tested for only 2 subjects, because of the possibility of severe reactions when highly acid or alkaline solutions were used. The reactions were similar in all subjects (table 2). The buffer solutions were applied to the intact or abraded skin for from twenty to twenty-four hours or until the reaction became intolerable. The abrasions were produced by scraping off the stratum corneum over an area of 0.3 by 0.3 cm., care being taken not to produce bleeding. One subject was tested with two, three and four times normal hydrochloric acid over the intact skin.

These results indicate that on the unbroken skin a concentration of three times normal hydrochloric acid—approximately 11 per cent (p_H —2)—is required before any reaction is noted. On abraded skin, however, the effect of the hydrochloric acid–aminoacetic acid buffer is marked at p_H 1.2, the subjective symptoms being severe for a short

TABLE 2.—*Reaction of Normal and Abraded Skin to Buffer Solutions of Varying p_H*

		Normal Skin		Abraded Skin	
p_H	Buffer Solution	Immediate Reaction	Delayed Reaction	Immediate Reaction	Late Reaction
—3.0	4 N hydrochloric acid	Burning in 15 min.; intolerable after 90 min.; wide erythematous flare; vesiculation	Crusted, scaling area; healing without a scar	.....	.....
—2.0	3 N hydrochloric acid	Wide erythematous flare after 90 min.	None	.....	.....
—1.0	2 N hydrochloric acid	None after 90 min.	None	.....	.....
1.2	Aminoacetic acid–hydrochloric acid	None	None	Burning and stinging subsiding in 30 min.; erythematous flare	Purulent crust; delayed healing; erythematous scar
2.0	Aminoacetic acid–hydrochloric acid	None	None	No symptoms, slight erythematous flare	Slight delay in healing
4.4	Acetate	None	None	None	None
7.2	Borate	None	None	None	None
9.6	Aminoacetic acid–sodium hydroxide	None	None	None	None
12.6	Aminoacetic acid–sodium hydroxide	Slight edema; superficial hydrolysis	Slight scaling	2 plus burning; erythematous flare	Slightly delayed healing; no scarring
12.79	Aminoacetic acid–sodium hydroxide	Marked edema, erythema, destruction of stratum corneum (2 hrs.), stinging and burning	Heavy nonpurulent crust, superficial atrophy	.....	.....
12.9	Aminoacetic acid–sodium hydroxide	Immediate burning, rapid destruction of stratum corneum (intolerable in 30 min.)	Heavy crust, permanent scar	.....	.....

time after the application and a slowly healing, slightly purulent ulcer and eventual scarring appearing. A slight reaction was also noted on abraded skin at p_H 2 (fig. 2 *B*).

On the alkaline side of the range the critical point at which keratolysis begins is noted at p_H 12.6. At this p_H a barely perceptible softening of the stratum corneum occurs. After application of a solution at p_H 12.79 a rapid but not extremely severe reaction is seen,

and at p_H 12.9 the stratum corneum is rapidly dissolved and a severe cutaneous response develops (fig. 2 *A*). On abraded skin the response at p_H 12.6 is slightly more marked than on the normal skin.

Action of Skin on p_H of Applied Buffer Solutions.—The following experiments indicate the effect which the skin has on the hydrogen ion concentration of buffered solutions applied to it for varying periods. The solutions were applied to the normal intact skin of the flexor surface of the forearm of 13 subjects in twenty-one experiments. The

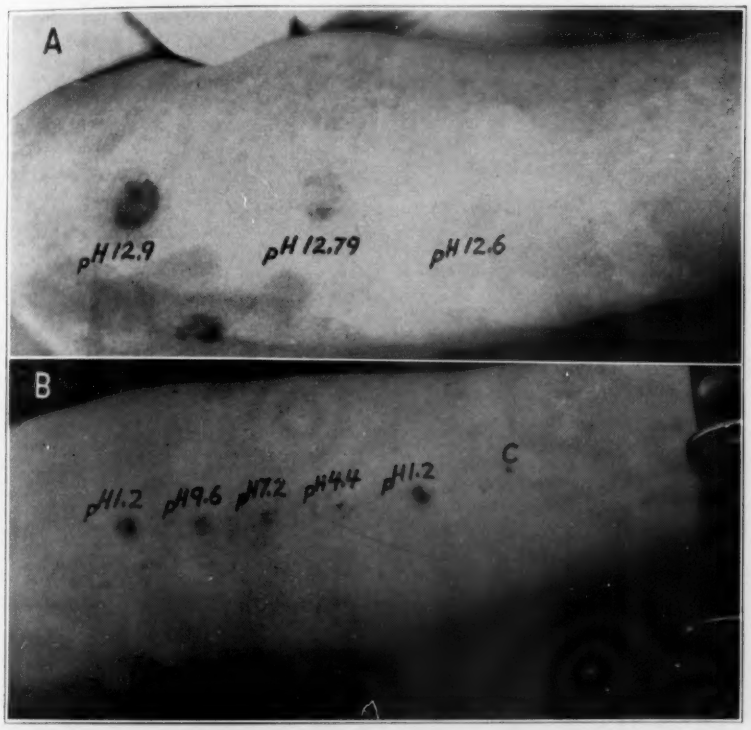

Fig. 2.—*A*, alkaline buffer solutions were applied for thirty minutes (photograph taken forty-eight hours later). Numbers represent the p_H of the solutions used. Below this series are the remains of similar tests performed one week previously. Only the evidence of the destructive effects of buffer p_H 12.9 remain visible. *B*, buffer solutions of different p_H were applied for eighteen hours on abraded skin. "C" represents the control site (photograph taken forty-eight hours after tests were applied).

experiments on the abraded skin were performed on 2 subjects in four experiments. Three-tenths cubic centimeter of the respective buffer solutions was used in all experiments (table 3).

These experiments indicated that the action of the skin on markedly acid and markedly alkaline buffer solutions is different, the acid solu-

TABLE 3.—*Change in p_H of Buffer Solutions in Contact with Skin*

Subject	p_H	Type of Buffer	Time in Contact, Hrs.	Final p_H	
				Normal Skin	Abraded Skin
D. P.	1.2	Aminoacetic acid–hydrochloric acid....	1	1.2	2.0
D. P.	1.2	Aminoacetic acid–hydrochloric acid....	20	1.4	...
B. S.	1.2	Aminoacetic acid–hydrochloric acid....	20	1.2	...
D. P.	1.2	Aminoacetic acid–hydrochloric acid....	20	1.4	3.3
A. B.	1.4	Aminoacetic acid–hydrochloric acid....	1	1.4	...
B. S.	1.4	Aminoacetic acid–hydrochloric acid....	1	1.4	1.9
D. P.	1.4	Aminoacetic acid–hydrochloric acid....	1	1.4	2.0
W. L.	1.4	Aminoacetic acid–hydrochloric acid....	1½	1.4	...
W. M.	1.4	Aminoacetic acid–hydrochloric acid....	2	1.4	...
J. W.	1.4	Aminoacetic acid–hydrochloric acid....	2	1.4	...
L. M.	1.4	Aminoacetic acid–hydrochloric acid....	2	1.4	...
A. B.	1.4	Aminoacetic acid–hydrochloric acid....	2	1.4	...
D. P.	1.4	Aminoacetic acid–hydrochloric acid....	14	1.4	4.4
D. P.	1.4	Aminoacetic acid–hydrochloric acid....	18	1.4	...
E. K.	1.4	Aminoacetic acid–hydrochloric acid....	20	1.4	...
N. I.	1.4	Aminoacetic acid–hydrochloric acid....	20	1.4	...
B. S.	1.4	Aminoacetic acid–hydrochloric acid....	20	1.4	5.2
G. V.	1.4	Aminoacetic acid–hydrochloric acid....	22	1.5	...
H. P.	1.4	Aminoacetic acid–hydrochloric acid....	24	1.6	...
B. S.	4.0	Acetate.....	1	4.0	...
D. P.	4.0	Acetate.....	1	4.0	...
B. S.	4.0	Acetate.....	20	4.2	...
D. P.	4.0	Acetate.....	20	4.2	...
B. S.	4.4	Acetate.....	1	4.4	4.4
D. P.	4.4	Acetate.....	1	4.4	4.4
B. S.	4.4	Acetate.....	1	...	5.9
B. S.	4.4	Acetate.....	18	4.4	4.4
D. P.	4.4	Acetate.....	18	4.4	4.6
D. P.	6.0	Phosphate.....	1	5.8	...
D. P.	7.2	Borate.....	14	6.8	...
B. S.	7.2	Borate.....	14	7.2	6.8
E. W.	9.6	Aminoacetic acid–sodium hydroxide...	½	9.1	...
B. S.	9.6	Aminoacetic acid–sodium hydroxide...	1	9.5	9.3
D. P.	9.6	Aminoacetic acid–sodium hydroxide...	1	9.4	9.1
W. L.	9.6	Aminoacetic acid–sodium hydroxide...	1½	9.3	...
J. W.	9.6	Aminoacetic acid–sodium hydroxide...	2	9.1	...
L. M.	9.6	Aminoacetic acid–sodium hydroxide...	2	9.5	...
A. B.	9.6	Aminoacetic acid–sodium hydroxide...	2	9.6	...
D. P.	9.6	Aminoacetic acid–sodium hydroxide...	26	7.8	...
D. P.	12.6	Aminoacetic acid–sodium hydroxide...	1	10.2	10.2
A. B.	12.6	Aminoacetic acid–sodium hydroxide...	1	12.4	....
B. S.	12.6	Aminoacetic acid–sodium hydroxide...	1	12.3	12.3
D. P.	12.6	Aminoacetic acid–sodium hydroxide...	1	12.1	12.2
W. M.	12.6	Aminoacetic acid–sodium hydroxide...	2	12.0	...
D. P.	12.6	Aminoacetic acid–sodium hydroxide...	14	8.9	...
B. S.	12.6	Aminoacetic acid–sodium hydroxide...	18	8.8	...
D. P.	12.6	Aminoacetic acid–sodium hydroxide...	18	8.8	...
D. P.	12.6	Aminoacetic acid–sodium hydroxide...	19	8.7	8.2
B. S.	12.6	Aminoacetic acid–sodium hydroxide...	20	8.5	...
D. P.	12.6	Aminoacetic acid–sodium hydroxide...	20	8.5	...
E. K.	12.6	Aminoacetic acid–sodium hydroxide...	20	8.4	...
N. I.	12.6	Aminoacetic acid–sodium hydroxide...	20	8.6	...
B. S.	12.6	Aminoacetic acid–sodium hydroxide...	20	8.3	8.9
G. V.	12.6	Aminoacetic acid–sodium hydroxide...	22	8.5	...
H. P.	12.6	Aminoacetic acid–sodium hydroxide...	24	8.4	...
B. S.	5.9	Distilled water.....	1	5.0	...
D. P.	5.9	Distilled water.....	1	5.4	...
D. P.	5.9	Distilled water.....	1	5.2	6.8
N. I.	5.9	Distilled water.....	20	5.9	...
B. S.	5.9	Distilled water.....	21	5.0	...
D. P.	5.9	Distilled water.....	21	5.8	...

tions at p_H 1.2, 1.4 and 4.4 changing hardly at all while the alkaline solution at p_H 12.6 showed a consistent decrease in from twenty to twenty-four hours to p_H 8.4 to 8.9.

In general, though the amount of change was not consistent, the acid solutions at p_H 1.2 and 1.4 underwent an increase in p_H much greater when applied to abraded skin than when applied to normal intact skin. The solutions on the markedly alkaline side showed approximately the same change whether applied to normal or to abraded skin.

It is to be noted that direct comparison of the effect of the skin on solutions of different buffer systems must be made with care. The systems vary in buffer capacity, and the same system may be a more efficient buffer at certain points of its curve than at others. However, in the solutions at p_H 1.4 and 12.6 the same buffer substance, aminoacetic acid, was present in exactly the same concentration. There was exactly the same amount of tenth-normal hydrochloric acid in the acid solution as there was tenth-normal sodium hydroxide in the alkaline solution.

Clinical Effect of Ointments in Which Buffer Solutions Were Incorporated.—Marchionini,[9] in applying his theory of the "acid mantle" of the skin as a protection against superficial infections, has employed acid lotions, powders and ointments in the treatment of intertriginous dermatophytosis and seborrheic processes. He reported good results in the treatment of seborrheic eczema with a salicylic acid–resorcinol lotion and an acid salve with a p_H of 2.3 or 4.6 (composition not given), together with interdiction of the use of soap.[10] In many cases various standard antiseborrheic measures were also employed. On a similar theoretic basis, Levin and Silvers [2a] employed a 1 per cent and a 2 per cent salicylic acid dusting powder with p_H of 5.7 and 4.85, respectively, in a water suspension, in the treatment of interdigital ringworm. In another report [3b] these writers indicated that they hope to evolve a rational treatment for eczema, based on their finding of changes in p_H of the surface of the skin.

We have seen no report in which the effect of alkaline preparations has been studied.

In the present study buffered ointments were prepared by incorporating four parts by weight of aminoacetic acid–hydrochloric acid buffer (p_H 2) or aminoacetic acid–sodium hydroxide buffer (p_H 9.6) in one part of cholesterolized petrolatum. The resulting cream was a satisfactory, smooth mixture, though some free fluid was noted when it was rubbed on the skin. The acid ointment was used in 33 cases of

9. Marchionini, A.: Säurebehandlung intertriginöser Epidermophytien, Dermat. Ztschr. **56**:248, 1929.

10. Marchionini, A.: Säuresalbenbehandlung seborrhoischer Hauterkrankungen des Gesichtes, Deutsche med. Wchnschr. **60**:934, 1934.

various dermatoses, and in 10 of these the alkaline ointment was applied to the opposite side of the body. The patients were instructed to apply the ointment freely twice daily or more. The results are summarized in table 4.

No more effect was noted on these dermatoses from the acid or the alkaline ointment than would be expected from the ointment base alone. We saw no evidence of adverse reaction to the alkaline ointment.

TABLE 4.—*Results of Treatment with Ointments Containing Acid and Alkaline Buffers*

	Effect of Acid Ointment p_H 2 Buffer			Effect of Alkaline Ointment p_H 9.6 Buffer		
Dermatosis	No. Cases	Average Period of Treatment, Wks.	Result	No. Cases	Average Period of Treatment, Wks.	Result
Neurodermatitis disseminata	1	4	Slight improvement	1	4	Slight improvement
Eczema of hands	5	3	1 improved 2 worse	2	3	1 improved 1 unchanged
Contact dermatitis	2	1	1 worse 2 no change 1 unchanged	2	1	1 worse 1 unchanged
Acne vulgaris	4	4	1 improved 3 unchanged	2	4	No change
Pyogenic sycosis	2	2	1 worse 1 unchanged	0		
Atopic dermatitis	2	3	Slight improvement	1	2	Slight improvement
Dyshidrosiform eruption of hands	5	4	2 improved 3 unchanged	2	2	1 improved 1 unchanged
Intertriginous dermatophytosis	5	3	2 improved 3 unchanged			
Rosacea	2	4	1 improved 1 unchanged			
Seborrheic eczema	2	4	1 improved 1 unchanged			
Psoriasis	2	4	No change			
Infantile eczema	1	1	No change			

A large volume of the buffer solution was used in the ointments, because it was found that cholesterolized petrolatum interferes with the electrolytic activity of salts mixed with it. It is probable that this is effected through the fine mechanical mixture which occurs. When only a small amount of buffer solution is used in the ointment, no change in p_H occurs in water into which some of the ointment is dropped. However, if the ointment is heated slightly, the oil and the buffer solution separate out and the latter can be recovered at its original p_H.

COMMENT

The results of the determination of the p_H of the cutaneous surface by this method again confirm the wide variation which may be noted on the skin of the same person or on the same portion of the cutaneous surface of different subjects. The portions of the cutaneous surface

tested were, in order of decreasing acidity, the flexor surface of the forearm, the extensor surface of the forearm, the flexor surface of the finger, the groin, the axilla, and the fourth interdigital space of the foot. The corresponding sides of the body show a close agreement of p_H in the same subject. When distilled water is left in contact with the skin for long periods (from eighteen to twenty-four hours), some tendency to an increase in p_H is noted. It is possible that this is due to the gradual collection of sweat and to its bacterial decomposition, but we have not yet studied this question.

The reported variable p_H of the cutaneous surface and our own results indicate that the free surface of the skin is the site of a variety of influences producing changes in acidity. There is no indication that the entire stratum corneum participates in this change in hydrogen ion concentration. Wilkerson [11] showed that the outer layer of the skin is true keratin, amphoteric and hence capable of ionizing both as an acid and as a base. He has determined the isoelectric point of stratum corneum obtained from scrapings of normal skin, calluses and exfoliated skin. This point, at which the movement of ground stratum corneum suspended in an electrical field is at a minimum, is at p_H 3.7. Wilkerson pointed out that this value is in close agreement with the average p_H for stratum corneum determined by Schade and Marchionini.[6] He stated that this value has a theoretic significance in the action of colloidal suspensions of a medicinal nature applied to the cleansed skin. The attraction depends on the charge on the suspended particle and the charge the skin assumes in contact with the solution. If the solution is acid, the skin would assume a positive charge, and positively charged particles in suspension would be repelled; if, however, the p_H of the solution is above the isoelectric point of skin, the skin would then tend to assume a negative charge and attract positively charged particles. It is obvious that this study by Wilkerson offers interesting theoretic possibilities in the explanation of the action of substances applied to the skin.

Of the various factors which might conceivably influence the p_H of the cutaneous surface, namely, excessive perspiration, ichthyosis, age, seborrhea and maceration, only the last mentioned seemed to have any regular relation in our cases. On toes on which there was macerated débris the surface p_H always tended toward an alkaline level.

The application of solutions of varying p_H to the skin demonstrated again the remarkable protection which the intact stratum corneum affords against acid solutions. A three times normal concentration of hydrochloric acid (p_H —2) was necessary before any irritation was seen.

11. Wilkerson, V. A.: The Chemistry of Human Epidermis: II. The Isoelectric Points of the Stratum Corneum, Hair, and Nails as Determined by Electrophoresis, J. Biol. Chem. **112**:329, 1935.

When, however, the continuity of the surface was broken, even superficially, acid buffer solution had a marked destructive effect at p_H 1.2, producing a slightly purulent slowly healing wound and definite scarring. On the alkaline side there was a sharp critical point between p_H 12.6 and 12.8 at which the keratolyzing effect became severe. Below p_H 12.6 no effect was seen. Also the effect of alkaline solutions on abraded skin was in our experiments no more marked than on normal skin. We have not as yet encountered any instance of sensitivity to solutions less alkaline than p_H 12.6, but this subject is being studied further.

The determination of sensitivity to alkali by means of patch tests must, we believe, be careful, since marked evaporation and consequent concentration of the salt occurs in twenty-four hours. In fact, it would seem that the interpretation of apparent allergic reactivity to varied concentrations of any substance dissolved in an aqueous or other volatile medium might be subject to question if the dissolved substance is capable of chemical irritant effects in higher concentrations. Designation of a test solution as 10 per cent, for instance, is correct only for a relatively short time after the patch test has been applied. It is possible that a method of applying solutions in patch tests in a more completely occluded state is worthy of further study as a method of determining cutaneous sensitivity.

We have not had the opportunity of comparing directly the determination of p_H of the cutaneous surface by use of an indicator and by electrolysis. The latter method undoubtedly makes possible finer determinations but is also subject to wide errors if not carefully controlled. In the presence of color, such as that of blood, the method which we have used becomes inaccurate; hence no determinations on colored fluids are recorded. It is our experience that the simple application of an indicator to the surface of the skin cannot furnish more than extremely gross evidence of the surface p_H. While some investigators have determined the p_H of the inner layers of the skin by means of indicators, it would seem that these findings must be regarded as only moderately accurate.

Another factor which is probably of importance in determining the hydrogen ion concentration within the skin is the fact that death of tissue or mechanical trauma produced by the introduction of electrodes or indicators undoubtedly produces changes in this regard. This would not apply to dead tissue, such as stratum corneum, but we believe that reported values for the inner layers of skin, while probably closely indicative of the true hydrogen ion concentration, may be subject to revision.

In the determinations of the "buffer" effect of the skin on solutions of different p_H, it is noted that the solution of p_H 1.2 was hardly affected by long contact with the skin, while the alkaline buffer at p_H

12.6 was regularly lowered to closely corresponding levels. Our series was not extensive enough to indicate whether significant variations in the alkali-neutralizing power of the skin are present in different subjects, as reported by Burckhardt [5]; there is no indication from our results thus far, however, that this is true. We cannot offer any explanation of the failure of the intact skin to influence the p_H of acid buffer solutions. It would be expected that the addition of even a small amount of perspiration to the solution would produce some change in p_H, and it is possible that some inhibition of sweating takes place. It seems evident that no appreciable chemical reaction of the keratin and the acid takes place. We are unable to state what role, if any, lipids or gases play in this situation.

Acid buffer ointment of p_H 2 was applied to 33 patients and alkaline buffer ointment of p_H 9.6 to 10 patients with a representative variety of common dermatologic conditions. From our initial experiments on the sensitivity of the skin to solutions of varying hydrogen ion concentration, we felt certain that no markedly deleterious effect would be noted from the application of material at these p_H levels, and we were anxious to test the theory of localization of certain dermatoses to alkaline regions by determining whether or not any flare-up followed the regular application of a moderately alkaline substance. The patients were instructed to apply the ointments liberally at least twice daily. It is certain that the areas to which the alkaline ointment was applied were not constantly maintained at the p_H of the contained buffer solution, both because the cutaneous surface tended to lower the p_H and because the medium of application, cholesterolized petrolatum, tended to inhibit the activity of the contained electrolyte. A few patients complained of some stinging from the acid ointment, but no reaction was noted from the alkaline substance.

We did not notice any significant variation in the clinical effect of the acid and the alkaline buffer ointment. There was no tendency for the alkaline ointment to produce a flare-up in any of the dermatoses in which it was employed. It is possible that the cholesterolized petrolatum and buffer, even with the latter in large excess, produced a mixture which was chemically relatively inert. When the mixture was separated, however, the buffer solution was recovered at its original p_H. It seems possible that cholesterolized petrolatum would similarly inactivate electrolytes on the surface of the skin, and the usefulness of this preparation in soap dermatitis, for instance, may in some measure be dependent on this faculty. One wonders whether the large amount of cholesterol and its esters in and on the surface of the skin may not be useful in this manner in protecting it from chemical insults.

We have had no means of comparing the ointment which we used with that employed by Marchionini,[10] since he gave no details of its preparation and it is apparently marketed as a proprietary remedy.

We do not wish to enter into an extended discussion of the relation of an alkaline p_H of the cutaneous surface to superficial infections and dermatitis. Cornbleet [12] has reviewed the evidence at length and concluded that much of the discussion regarding the effect of the acid corneous layer in resisting infection by means of its acidity per se is highly theoretic and unproved. He has shown that sweat is a good culture medium for yeasts and staphylococci at p_H from 3 to 8. Peck [13] has shown that buffer substances may be effective in inhibiting the growth of a fungus by keeping the organism from producing the p_H at which it grows best.

It must be pointed out that while there is no question that the most common site of dermatophytic involvement, namely the fourth interdigital space of the foot, has a somewhat higher p_H than any other portion of the cutaneous surface when maceration is present, there is no absolute proof that the higher p_H is the primary cause of this localization and not entirely secondary to bacterial ammoniacal protein decomposition. It is possible that a constantly maintained slightly alkaline p_H may be a factor in producing a more ready local sensitization to fungi, as has been suggested by Burckhardt in the case of nickel sensitivity, but further study is necessary to determine this.

SUMMARY

1. The intact skin is able to withstand solutions of p_H ranging from -2 (three times normal hydrochloric acid) to p_H 12.6.

2. Abraded skin reacts violently to solutions having a p_H of 1.2, a slightly purulent ulcer being produced, healing slowly and leaving a scar.

3. The response of abraded skin to alkaline solutions up to and including p_H 12.6 is no worse than that of intact skin.

4. Acid solutions applied to normal skin show almost no tendency to a rise in p_H.

5. Alkaline solutions show a definite and regular fall in p_H on contact with the skin.

6. The standard patch test is an inefficient means of maintaining the concentration of an applied solution.

7. The p_H of the surface of the skin shows wide variations in different areas and in different subjects. The average p_H for each region is as follows: the flexor surface of the forearm, 5.1; the extensor sur-

12. Cornbleet, T.: Self-Sterilizing Powers of the Skin: V. Are They Endowed by the Surface Acid? Arch. Dermat. & Syph. **28**:526 (Oct.) 1933.

13. Peck, S., and Rosenfeld, H.: The Effects of Hydrogen-Ion Concentration, Fatty Acids, and Vitamin C on the Growth of Fungi, J. Invest. Dermat. **1**:237 (Aug.) 1938.

face of the forearm, 5.3; the flexor surface of the index finger, 5.4; the groin, 5.7; the axilla, 5.8, and the fourth interdigital space of the foot, 6.5.

8. Keratolysis of the stratum corneum always occurs at a p_H above 12.6; at p_H 12.8 it is rapid and severe.

9. Buffer solutions of p_H 2 and 9.6 incorporated in cholesterolized petrolatum have not had any regular effect on various dermatoses in 33 patients.

ABSTRACT OF DISCUSSION

DR. C. GUY LANE, Boston: For the past two years at the Massachusetts General Hospital Dr. Irvin H. Blank has been studying the hydrogen ion concentration of the cutaneous surface. He spent some time in perfecting the technic and ascertaining measurements on normal skin. Buffer action has to do with the resistance to change of p_H exhibited by a sloution when it is subjected to gain or loss of acid or alkali. The usual technic has measured not the buffer action of the skin but the ability of the solution to resist change of p_H when it is subjected to gain or loss of the alkali or acid supplied by the skin or possibly by the carbon dioxide in the air. Dr. Blank has not found any entirely satisfactory method of measuring the so-called buffer action of the skin. To measure the p_H of the cutaneous surface he has used a glass electrode with the vacuum tube potentiometer and 0.1 per cent sodium chloride solution in distilled water to moisten the skin. He has changed the p_H of this solution by the addition of small amounts of hydrochloric acid or sodium hydroxide. Within certain limits there has been very little change in the p_H of the cutaneous surface, but if the solution is altered to a higher or lower hydrogen ion concentration there is definite variation in the hydrogen ion concentration of the cutaneous surfaces. Just before I left he showed me a table of measurements made on both arms of the subject. He used on one arm a solution with a p_H of 5, repeating the test in two hours. On the other arm he used originally a solution with a p_H of 5 and at the end of two hours solutions of varying p_H (3, 4, 5, 6, 8, 9 and 10). Only those solutions which had a p_H below 4 or above 9.5 made any specific variation in the hydrogen ion concentration as measured.

In measuring over a period of hours the change in p_H of a solution added to the cutaneous surface he used both continuous contact and intermittent contact but arrived at no satisfactory conclusion because of three obvious errors, one resulting from the evaporation of the solution, the second from alteration of the p_H by the carbon dioxide of the air and the third from variation in the original acidity of the individual cutaneous surface. Only large variations in the rate of change as noted by this method are of importance. It seems possible that the use of such apparatus as Dr. Pillsbury described may be of distinct value and may contribute definitely to the study of important physiologic changes in the skin.

CHOLESTEROL BALANCE AND LOW FAT DIET IN PSORIASIS

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Psoriasis has been a subject for dermatologic research since the disease first became known. Excellent clinical descriptions and exact histologic studies of all phases of the disease have been recorded, but the cause remains unknown and the treatment is unsatisfactory. A detailed review of the voluminous literature on psoriasis is not necessary in an experimental paper of this type. Grütz and others have expressed belief that disturbances of fat metabolism cause psoriasis and that a low fat diet is beneficial in its treatment. This study helps to evaluate these assertions and shows certain other facts concerning the disease. Only those patients who showed definite clinical and histologic evidence of psoriasis were included in the group studied.

Rosen, Rosenfeld and Krasnow [1] concluded that hypocholesteremia existed in psoriasis, while Grütz and Bürger [2] found marked hypercholesteremia. There are several such contradictions in the literature.

It is generally accepted that psoriatic scale has a high cholesterol content. Some observers have reasoned that it followed that the blood of patients with psoriasis also would have a high cholesterol content. Single determinations of cholesterol showed great variation; so Grütz and Bürger offered a cholesterol tolerance test to show that fat metabolism was disturbed in psoriasis. In their hands there was not always an increase in the cholesterol content of the blood, but they always found a shifting of the relationship of the lipoid fractions. The determinations of cholesterol were made on the serum or plasma, because the lipoids in the blood corpuscles do not take part in changes of composition of the lipoids in the plasma. Citrated or oxalated blood was not used because dilution of the plasma with water from blood corpuscles caused an error in the determinations.

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1. Rosen, I.; Rosenfeld, H., and Krasnow, F.: Studies in Psoriasis, Arch. Dermat. & Syph. **35**:1093-1100 (June) 1937.

2. Grütz, O., and Bürger, M.: Die Psoriasis als Stoffwechselproblem, Klin. Wchnschr. **12**:373-379 (March 11) 1933.

CHOLESTEROL TOLERANCE TEST

The fasting subject was given 5 Gm. of cholesterol in 100 cc. of olive oil, and the blood for investigation was withdrawn at two, four, eight and twenty-four hour intervals thereafter. Grütz and Bürger required several estimations of lipoid fractions in 50 cc. specimens of blood withdrawn at least five times in twenty-four hours. The procedure obviously is complicated and time consuming. It was decided to reduce the quantity of the specimens to 10 cc. of blood, withdraw them at the same intervals and study the changes in cholesterol alone.

Method of Determining Cholesterol in the Plasma.—Two cubic centimeters of plasma was mixed with about 65 cc. of "alcohol-ether" (3 parts of dehydrated alcohol and 1 part of ether). The mixture was shaken thoroughly and heated to the boiling point in a water bath. It was shaken frequently to prevent overheating. The mixture was cooled to room temperature and made up to 100 cc. with "alcohol-ether." It was mixed thoroughly and centrifuged or filtered. Ten cubic centimeters of the filtrate was placed in a glass evaporating dish and evaporated just to dryness in the water bath. The residue was extracted three times with 2.5 cc. portions of dry chloroform. The chloroform extract was placed in a 10 cc. cylindric glass container, and 2 cc. of acetic anhydride and 6 drops of concentrated sulfuric acid were added. The mixture was then made up to a volume of 10 cc. with dry chloroform. The ingredients were mixed thoroughly and allowed to stand twelve to fifteen minutes, until a green color developed, and the mixture was compared with a standard in a colorimeter. The standard contained 0.5 mg. of cholesterol, 2 cc. of acetic anhydride and 6 drops of concentrated sulfuric acid made up to 10 cc. with dry chloroform. Several readings were made and the average was taken. The following formula was used:

$$\frac{0.5 \text{ Milligrams cholesterol in standard} \times 10 \text{ standard setting} \times 500}{\text{Colorimeter reading of unknown}} = \text{milligrams of cholesterol per hundred cubic centimeters of plasma.}$$

Results.—The normal figures for cholesterol in blood range from 150 to 200 mg. per hundred cubic centimeters of plasma or serum. Grütz and Bürger found the average value of total cholesterol in the serum in patients with psoriasis was 51 per cent above that of normal patients. Only 1 of their 21 patients had a normal value. Grütz and Bürger found that an absolute or relative increase of the total fat and any of its components was greater in healthy subjects after the cholesterol tolerance test. My observations showed a greater relative and absolute increase in patients with psoriasis than in those with other diseases. They also found that the increase in the cholesterol content of the blood caused by ingestion of cholesterol and olive oil was overcome in twenty-four hours in healthy patients and that there was a tendency to actual decrease in psoriatic subjects. My studies showed this to be true in patients with other diseases, but that the cholesterol balance in psoriatic patients did not return to normal after twenty-four hours. Grütz and Bürger's healthy subjects showed an increase in cholesterol

Results of Low Fat Diet in Psoriasis

Case		Weeks of Observation									Final Observation
		2	4	6	8	12	16	20	24	30	
1	Cholesterol*.....	189	140	200	225	229	352	320	325	325	Improvement during hospitalization then condition remained stationary until loss of body weight and grew much worse thereafter
	Body weight†.....	140	140	140	140	140	140	140	140	131	
	Change in psoriasis	Markedly improved	Improved	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Much worse	
2	Cholesterol.....	139	166	147	139	203	233	...	...	...	Steady improvement; eruption involuted in 7 weeks
	Body weight.....	230	198	197	195	197	195	...	...	...	
	Change in psoriasis	Markedly improved	Markedly improved	Lesions almost gone	No eruption	No eruption	No eruption				
3	Cholesterol.....	208	222	200	179	208	250	182	205	240	Improvement during hospitalization and in early weeks; condition stationary thereafter
	Body weight.....	177	177	176	174	173	171	170	170	168	
	Change in psoriasis	Markedly improved	Markedly improved	Stationary	Stationary	Improved	Stationary	Stationary	Stationary	Stationary	
4	Cholesterol.....	238	154	138	120	119	119	126	116	130	Steady improvement with short stationary periods; eruption involuted in 24 weeks
	Body weight.....	120	113	120	118	116	115	111	109	108	
	Change in psoriasis	Improved	Improved	Improved	Improved	Lesions almost gone	Stationary	Slightly improved	No eruption	No eruption	
5	Cholesterol.....	171	257	250	198	175	182	...	...	...	Early improvement; stationary periods with short exacerbations and remissions
	Body weight.....	115	115	113	115	112	114				
	Change in psoriasis	Improved	Improved	Improved	Stationary	Stationary	Stationary				
6	Cholesterol.....	123	208	250	161	206	...	...	...	...	Remissions and exacerbations during entire time
	Body weight.....	104	104	102	102	105					
	Change in psoriasis	Stationary	New lesions	Stationary	Stationary	New lesions					
7	Cholesterol.....	166	139	188	125	160	156	170	125	...	Improvement with stationary periods; general improvement
	Body weight.....	133	129	128	129	127	132	128	122	...	
	Change in psoriasis	Stationary	Improved	Improved	Stationary	Improved	Stationary	Stationary	Markedly improved		
8	Cholesterol.....	158	135	129	213	...	...	...	...	...	Steady improvement
	Body weight.....	155	156	157	150						
	Change in psoriasis	Stationary	Improved	Improved	Improved						
9	Cholesterol.....	471	390	438	379	490	242	...	...	...	Early improvement; condition later stationary
	Body weight.....	143	142	141	141	143	143				
	Change in psoriasis	Improved	Improved	Improved	Improved	Improved	Stationary				

10	Cholesterol.....	130	150	184	166	151	160	190	166	...	No eruption in 6 wks.; eruption reappeared when 50 Gm. of fat added; disappeared in 2 wks. when fat reduced; patient hospitalized for 4 mos.
	Body weight.....	149	150	150	148	143	143	141	137		
	Change in psoriasis	Improved	Improved	No eruption	No eruption						
11	Cholesterol.....	174	234	208	139	121	...	...	...	...	Steady improvement
	Body weight.....	124	124	122	122	120					
	Change in psoriasis	Improved	Improved	Improved	Improved	Improved					
12	Cholesterol.....	201	347	210	221	...	...	...	...	...	Steady improvement during diet; new lesions appeared when diet was disregarded
	Body weight.....	146	145	145	143						
	Change in psoriasis	Improved	New lesions	Improved	Improved						
13	Cholesterol.....	161	161	138	116	117	125	182	...	...	Improvement during diet; new lesions appeared when diet was disregarded
	Body weight.....	127	124	122	122	127	122	122			
	Change in psoriasis	Improved	New lesions	New lesions	Improved	Improved					
14	Cholesterol.....	291	152	325	190	178	...	...	...	...	Slight remissions and exacerbations
	Body weight.....	178	168	168	166	167					
	Change in psoriasis	Improved	Improved	New lesions	Improved	Stationary					
15	Cholesterol.....	161	195	182	166	170	...	...	...	...	No change
	Body weight.....	148	144	143	139	139					
	Change in psoriasis	Stationary	Stationary	Stationary	Stationary	Stationary					
16	Cholesterol.....	168	189	149	202	...	...	...	...	...	No change
	Body weight.....	84	83	79	81						
	Change in psoriasis	Stationary	Stationary	Stationary	Stationary						
17	Cholesterol.....	200	200	199	192	150	...	...	...	...	Improvement during diet; new lesions appeared when diet was disregarded
	Body weight.....	134	135	137	136	139					
	Change in psoriasis	Improved	Improved	Improved	Improved	New lesions					
18	Cholesterol.....	162	134	163	168	164	225	...	...	...	Steady improvement
	Body weight.....	120	119	122	123	123	141				
	Change in psoriasis	Improved	Improved	Improved	Improved	Improved	New lesions				
19	Cholesterol.....	297	390	390	312	...	178	...	...	...	Steady improvement
	Body weight.....	152	150	148	150	...	123				
	Change in psoriasis	Improved	Improved	Improved	Improved	.....	Improved				
20	Cholesterol.....	200	271	240	...	...	...	...	...	...	No change
	Body weight.....	140	140	139							
	Change in psoriasis	Stationary	Stationary	Stationary							
21	Cholesterol.....	172	185	200	200	...	...	...	...	...	No change
	Body weight.....	165	165	165	166						
	Change in psoriasis	Stationary	Stationary	Stationary	Stationary						
22	Cholesterol.....	155	156	150	...	123	...	...	...	...	Improvement
	Body weight.....	34	33	33	...	36					
	Change in psoriasis	Improved	Stationary	Stationary	.....	Improved					

* Cholesterol in mg. per hundred cubic centimeters of plasma.
† Body weight in pounds.

of 53 per cent after four hours, 39 per cent after eight hours and 9 per cent after twenty-four hours. My patients with other diseases showed an increase of cholesterol of 7 per cent after four hours and of 11 per cent after eight hours and a return to the starting value after twenty-four hours. Their psoriatic patients showed an increase of cholesterol of 18 per cent after four hours, 16 per cent after eight hours and 0.6 per cent after twenty-four hours, while mine showed an increase of 11 per cent after four hours, 19 per cent after eight hours, and 7 per cent after twenty-four hours. These two independent observations are contradictory.

Tests made during fasting showed an average of 213 mg. of cholesterol per hundred cubic centimeters in 35 patients with psoriasis and of 183 mg. in 29 patients with other diseases. These figures showed that hypercholesteremia did not generally exist in the persons with psoriasis studied. It is true that some persons with psoriasis showed hypercholesteremia, but others showed hypocholesteremia. Variations were also noted in persons with other diseases.

The curves obtained in the cholesterol tolerance test showed wide variation. The effect of the intake of cholesterol on the cholesterol in specimens of blood taken during the test was comparatively slight. The cholesterol content of the blood of psoriatic subjects was generally slightly higher than that of patients with other diseases. Psoriatic patients showed comparatively more cholesterol in the blood after the two hour specimen had been taken and retained the cholesterol in the blood for a longer period. It was evident that the individual variations were too great and the curves too irregular to justify placing any value on the test. No certain type of curve was of value in determining whether or not a given subject would respond favorably or unfavorably to a diet low in fat. The cholesterol tolerance test did not show that a disturbance of fat metabolism exists in patients with psoriasis.

LOW FAT DIET IN PSORIASIS

Those observers who favor a disturbance of fat metabolism as the cause of psoriasis have stated that the disease is not rarely associated with xanthomatosis and diabetes. This association was not seen in my cases. They have expressed the belief that the reason psoriasis is seen much more often in northern climates than in the tropics is that persons in northern climates eat more fat; and that this explains also why psoriasis is often more severe in winter.

Pulay [3] and other authors have expressed the belief that in psoriasis as in diabetes the assimilation of fat is upset and a fat-free regimen is necessary for the proper care of the patient, but that the disease is not

3. Pulay, E.: Le "psoriasis vulgaris" et son traitement, Bull. Soc. franç. de dermat. et syph. **43**:1508-1521 (July) 1936.

caused by a disturbance of fat metabolism. Pulay stated the opinion that the disturbance of fat metabolism is important in the pathogenesis of psoriasis but not in its causation.

Selection of Subjects.—Patients who could not be observed closely for six weeks or longer were not included in this group. Persons who admitted that they would not adhere or had not adhered to the diet were not considered. Elderly patients, pregnant women, growing children and farmers who did manual labor often could not be persuaded to go on a low fat diet. Those who were not intelligent enough to follow a diet were also eliminated.

The Diet.—The fat was limited to 20 Gm. daily for adults and 10 Gm. daily for children while they were in the hospital. The caloric requirements were met by adding carbohydrate and protein. Patients need not lose weight on such a diet, and no ill effects were noted from the reduction in fat.

A weighed diet was considered impractical in the home, so the patients were given the following measured low fat diet. If this diet was followed there would be only about 20 Gm. of fat in the total daily intake of food. The patients were given no other treatment when they were on the diet.

SAMPLE LOW FAT DIET

Breakfast

1. Fruit: 1 medium orange, ½ grapefruit or ½ banana
2. Bread: 2 slices, ½ inch (1.3 cm.) thick, toasted or plain
3. Butter: only 1 teaspoonful
4. Cereal: ⅔ to 1 cup of cornmeal, farina, cream of rye, oatmeal or cream of barley (dry cereal may be used)
5. Sugar: 1 tablespoonful
6. Skim milk: 1 glass
7. Jam or marmalade: 1 heaping tablespoonful
8. Beverage: tea or coffee, without cream

Dinner

1. Vegetable, cooked or raw: ½ cup of celery, cabbage, tomatoes, string beans, lettuce, asparagus, spinach, Swiss chard or broccoli (do not add cream or butter; if the vegetable is used as a salad, mayonnaise or French dressing made with liquid petrolatum) may be used
2. Potato: one generous serving (¾ cup) of mashed, boiled, baked or escalloped (Do *not* fry!)
3. Lean meat: 1 slice 2½ by 2½ by ½ inch (6.4 by 6.4 by 1.3 cm.) of beef, veal, lamb, chicken or fish, broiled, boiled or roasted (do not fry)
4. Bread: 2 slices ½ inch (1.3 cm.) thick, white, graham or rye
5. Butter: only 1 level teaspoonful
6. Jam or honey: 1 tablespoonful
7. Skim milk: 1 glass
8. Sugar: 1 tablespoonful

9. One of the following: 1 medium-sized apple, ½ cup jello, ½ cup grapes, ½ cup rice or tapioca pudding (made without egg yolk) or ½ cup sherbet or ice
10. One of the following: 2 plain sugar cookies (made without fat), 2 graham crackers or 2 "uneeda" crackers
11. One of the following: 7 medium-sized dates or ⅓ cup of raisins
12. Beverage: tea or coffee, without cream

Supper

1. Vegetable, cooked or raw: ½ cup of carrots, beets, peas, turnips, rutabagas, squash or onions
2. One of the following foods: 1 generous serving (¾ cup) of potato, rice, macaroni, noodles or sweet corn
3. Bread: 2 slices ½ inch (1.3 cm.) thick
4. Butter: only 1 level teaspoonful
5. Skim milk: 1 glass
6. Sugar: 1 tablespoonful
7. Jam or jelly: 1 tablespoonful
8. Cottage cheese: ¼ cup (without cream)
9. Dessert: 1 serving of any of the following fruits: peaches, pears, apples, berries, pineapple (stewed, canned or fresh)
10. Plain sugar candy (no chocolate or nuts) 1 ounce (28.35 Gm.) or ¾ cup of sweetened grape juice
11. Beverage: tea or coffee, without cream

The following foods should be avoided:

Cream, ice cream, butter (except as mentioned), salad oils, lard, vegetable fats, bacon, pork, fatty meats and fish, pastries, chocolate, nuts, gravies, cheese (except cottage cheese), all fried foods, eggs, inner organs, such as liver, brain, kidneys or sweetbreads, creamed foods, foods prepared with butter or eggs, oils, such as olive oil or cod liver oil, olives, spices, cakes, pies and cocoa.

The following foods may be added if the patient is still hungry:

Bread, jam, jelly, honey, marmalade, syrup, sugar, flour, cornstarch, cereals, dates, raisins, fruits and vegetables.

Results.—Psoriasis entirely disappeared in 3 cases in six, seven and twenty-four weeks, respectively, after institution of a low fat diet. The eruption improved greatly in 3 cases, but new lesions occurred when the diet was disregarded. In 2 cases there was improvement during hospitalization and the psoriasis remained stationary thereafter. In 1 case there was great improvement during hospitalization, but slight remissions and exacerbations occurred afterward. In 6 cases there was steady improvement while the low fat diet was followed. In 4 cases there was no change in the eruption. Psoriasis became definitely worse in 1 case, and in 2 cases there were short exacerbations and remissions while the low fat diet was used.

Psoriasis disappeared or was definitely improved in 15 cases, 68 per cent, while the low fat diet was followed. The eruption did not change

in 6 cases, 27 per cent, during ingestion of the same diet. The disease became more severe in only 1 case, 5 per cent, and this took place after a sudden loss of 9 pounds (4 Kg.) in body weight.

The lesions usually disappeared from the face first, then from the trunk, genitalia and scalp and from the extremities last. The pruritus subsided first; then the scale would be lost, the papules become macules, the erythema fade and finally the slight erythema or pigmentation at the sites of old lesions be lost. The heavy infiltrated plaques of psoriasis were the last to change, and the small guttate papules disappeared first. However, no one type of psoriasis responded better than another to the diet; there were merely longer or shorter periods before improvement appeared.

Hospitalization seemed to be the most important factor in determining the effect of the diet on psoriasis. Schamberg [4] observed the benefit of hospitalization when he did his work on low protein diet. It is general knowledge that psoriatic subjects seem to improve more rapidly on any treatment if it is carried out under a strict hospital regimen. During hospitalization the food was weighed, and the eruption showed the greatest improvement. The food was not weighed after the patient left the hospital; the patient merely avoided the designated foods and consequently probably took more fat than was allowed.

The effect of the low fat diet apparently was not influenced by the age of the patient, the duration of the psoriasis or the relative obesity or thinness of the patient. One of the most favorable results occurred in the case of an obese woman aged 76 years, and another in that of a thin girl aged 4 years.

The amount of cholesterol in the blood had no prognostic value. The cholesterol varied a great deal whether the psoriasis remained stationary, disappeared or became more marked.

A slight loss in or maintenance of body weight seemed to have a favorable influence on the eruption in most cases. Patients who were on the government relief rolls and whose food could be more easily regulated generally responded more favorably than those who were from rural communities, where no strict food regulations could be enforced. When the diet was positively controlled the results were always better.

A low fat diet was of definite benefit in most cases of psoriasis. The results of this study show that disturbances of fat metabolism probably are not the cause of psoriasis, nor will a low fat diet cure the disease in most cases. Similar improvement has been noted when other diets have been given. The favorable results obtained in this

4. Schamberg, J. F.: The Dietary Treatment of Psoriasis, J. A. M. A. **98:** 1633-1635 (May 7) 1932.

group of cases may be explained on the basis of a general realinement of metabolism and tissue function, which could be secured in many different ways.

SUMMARY

Hypercholesteremia did not generally exist in the cases of psoriasis studied. The effect of the intake of cholesterol on the cholesterol content of specimens of blood taken during the cholesterol tolerance test was comparatively slight. The individual variations were too great and the curves shown by the cholesterol tolerance test too irregular to justify placing any value on the test. No certain type of cholesterol tolerance curve was of value in determining whether or not in a given case psoriasis would respond favorably or unfavorably to a low fat diet.

A low fat diet was of definite value in most cases of psoriasis (68 per cent). Hospitalization or positive control of the patient seemed to be the most important factor in determining the effect of the diet on the disease. The favorable effect of the diet may be explained on the basis of a general realinement of metabolism and tissue function rather than on the basis of disturbed fat metabolism. The effect of ingestion of vitamins on psoriasis will be reported in a future publication.

ABSTRACT OF DISCUSSION

DR. RICHARD J. BAILEY, Spokane, Wash.: Since the report of Grütz and Bürger in 1933, there has been an increasing tendency to accredit the favorable influence of various methods of treatment of psoriasis to their possible corrective effect on disorders of fat metabolism.

The principles presented to indicate that psoriasis is a disturbance of the fat metabolism are essentially the following findings and assumptions: (1) that the lipoid content of the blood, particularly the cholesterol content, was elevated in one group of psoriatic patients in comparison with a group of subjects without psoriasis; (2) that psoriasis tends to appear in some of the sites involved by xanthoma tuberosum; (3) that the secretions of the adrenal cortex, the anterior lobe of the pituitary and thyroid perhaps favorably influence lipoid metabolism; (4) that even sarsaparilla, because of its safranine content, has a special affinity for cholesterol, and its ingestion tends to restrict excesses, and (5) that vitamins B, C and D separately in some way influence fat metabolism.

These principles do not rest on too secure a foundation, depending as they do mainly on favorable therapeutic response and often not on thoroughly controlled laboratory and clinical data.

As xanthomatosis is at the present time undergoing intensive investigation, it offers a comparative study, particularly in regard to cholesterol determinations. Recently Fritz Schaaf (On the Experimental Production of Xanthomas in Laboratory Animals, *J. Invest. Dermat.* **1**:11 [Feb.] 1938) stated on the basis of reviewed knowledge of the cholesterol content of the blood that two important etiologic factors are indicated in the production of xanthoma: (1) icterus in conjunction with hepatic disturbance and (2) hypercholesteremia. These, of course, may be related, and they are not necessarily antagonistic to the theory of disturbed metabolism in the cell itself.

He further stated that often too much emphasis has been placed on a single factor, thus leading to the neglect of other equally important factors, and that in the absence of hypercholesteremia other pathologic changes in the fats in the content of blood must be accurately demonstrated.

These statements are particularly pertinent in the study of similar factors in psoriasis, and before the theory that disturbed fat metabolism is the etiologic factor in this disease is accepted the establishment of three premises seems requisite: (1) that the studied control group of so-called normal persons be sufficiently large so that abnormal states of fat metabolism may be accurately defined and recognized; (2) that such abnormal changes at some time be demonstrated in all psoriatic patients, and (3) that measures aimed at correcting these abnormal states be proved to be entirely responsible for a favorable therapeutic effect.

The cholesterol tolerance test has been suggested as a means of detecting abnormalities, but so far does not lend itself to accurate conclusions in individual cases.

Dr. Madden has presented the largest reported series evaluating the cholesterol tolerance test and the low fat diet in psoriasis.

In comparing this diet with the low protein diet of Schamberg, he stated that the benefit of supervision in the hospital is an important factor in both. The further comparison that the low fat diet is also a low protein diet and may be effective on that basis has been suggested and deserves consideration.

At present I am observing two groups of young ambulatory psoriatic patients. Each is receiving viosterol in doses containing 250,000 to 300,000 U. S. P. units of vitamin D daily. One group is without dietary restriction and the second is using a low fat diet exactly like that described in Dr. Madden's paper. The persons in the latter group are showing a more rapid involution of lesions, but as they have only been under observation for one month, accurate evaluation is not possible.

I believe Dr. Madden has shown that the low fat dietary regimen in itself is not sufficient to control the manifestations of psoriasis. He found the results of cholesterol tolerance tests to be distinctly different from those previously reported; in addition he has presented laboratory studies discrediting other older theories. Dr. Madden is to be congratulated for a timely and valuable contribution to the study of psoriasis.

DR. JOHN F. MADDEN, St. Paul: Bürger and Grütz based their conclusions on a small number of cases, especially on 1 case of psoriasis in a patient who also had xanthoma and diabetes. In my cases of psoriasis I have seen no association with xanthoma or diabetes.

JAUNDICE OCCURRING DURING THE TREATMENT OF SYPHILIS

C. GUY LANE, M.D.
BOSTON

Jaundice as a complication of syphilis has long been known. The relationship was apparently pointed out first by Paracelsus, early in the sixteenth century. An occasional reference appears in the literature between this time and 1853, when Gubler published a report of 7 cases of what he called true syphilitic jaundice. Ricord had described jaundice in 2 cases of early syphilis but had recorded them merely as observations. A little later Lanceraux reported 20 more cases. After the institution of modern arsenical treatment, in 1910 and 1911, a number of cases of so-called arsphenamine jaundice were reported abroad. Since that time much literature has accumulated on this interesting phase of syphilis and its treatment.

More recently Wile and Sams discussed the subject thoroughly from the standpoint of 91 cases of syphilis of the liver and 56 cases of jaundice occurring during treatment at the University Hospital [Michigan] clinic. They found that jaundice occurred as a manifestation of syphilis of the liver in only 0.18 per cent of cases of syphilis. Jaundice, however, occurred in 1.35 per cent of the cases in which arsenic was used, thus incriminating this drug as a potent causal factor. They commented on the occurrence of catarrhal jaundice in many cases at a time when the bulk of the post-therapeutic jaundice appeared, but did not find evidence to support the view held by Milian and others, regarding jaundice as evidence of hepatorecurrence. They admitted much difficulty in determining the exact cause of the jaundice and emphasized the importance of an accurate history in differentiation.

Sager reviewed the cases of jaundice occurring at Mount Sinai Hospital, New York. He emphasized arsphenamine as a factor in paratherapeutic jaundice and compared the jaundice in his series with that appearing in nonsyphilitic persons as catarrhal jaundice, yellow atrophy and cirrhosis.

Soffer, at Johns Hopkins Hospital, found 158 cases of jaundice among 18,250 cases in which antisyphilitic treatment was given and reported complete studies of the blood in 32 cases.

Read at the Sixty-First Annual Meeting of the American Dermatological Association, Inc., Del Monte, Calif., June 10, 1938.

INCIDENCE

From 1929 to 1935 there have been 100 cases of jaundice at the dermatosyphilologic clinic of the Massachusetts General Hospital, appearing among 3,186 new cases of syphilis in these years. There have been 51,241 injections of an arsphenamine given at the hospital in this time, so that in this clinic jaundice occurred in 3.2 per cent of cases of syphilis and after 0.2 per cent of injections of arsphenamine.

The standard course of treatment during this time has been ten injections of arsenic, preferably arsphenamine, followed by fifteen injections of a bismuth preparation. Three such courses are given in cases of early primary syphilis (thirty injections of arsphenamine and forty-five of the bismuth preparation) and four in cases of secondary and other types (forty of arsphenamine and sixty of the bismuth preparation), unless changes in the procedure have been required in an individual case by reason of untoward symptoms or persistence of a positive serologic reaction or symptoms in the central nervous system. During this time a rest period of one month has been allowed between courses.

AGE

In these 100 cases 3 patients were below 10 years of age, 9 between 10 and 19, 22 between 20 and 29, 26 between 30 and 39, 22 between 40 and 49, 16 between 50 and 59 and 2 over 60. It is natural that in 70 cases the condition should have occurred between 20 and 50. There were 57 male and 43 female patients in the group.

Eighteen patients were 50 or over. With all but 4 of these treatment had been started with a bismuth preparation, and the majority had two series of the bismuth compound and one of arsphenamine. Only 1 had four series of treatments. In 10 cases the course of bismuth treatment was interrupted by the jaundice. In 14 cases the jaundice lasted seven weeks or less. Sixteen were cases of late disease; in only 2 were active cutaneous lesions present. There were 2 cases of secondary syphilis. In all but 3 the interval since the last treatment, with either arsphenamine or the bismuth preparation, was less than three weeks, so that hepatorecurrence was unlikely.

STAGE OF DISEASE

It is worth noting that in 11 of the cases the disease was congenital, in 9 primary, in 25 secondary and in 55 late, with involvement of the central nervous system in 14.

DURATION

Table 1 shows the duration of jaundice. In 10 cases it was impossible to determine the end of the jaundice. It is probable that the

jaundice lasted longer than is indicated in the table, because the patients were undoubtedly jaundiced before it was noted in the records. In only 11 cases was jaundice present longer than eight weeks. Of special interest are the 3 cases in which jaundice was noted twice during treatment and the 4 cases of jaundice of fifteen or sixteen weeks' duration. The latter group comprised cases of late disease treated with a series of injections of a bismuth preparation interrupted by the jaundice. In none were more than ten injections of neoarsphenamine and twenty-two of the bismuth preparation given.

SYMPTOMS

The prodromal symptoms varied greatly. In cases of mild involvement the patient simply noticed jaundice with perhaps a little malaise.

TABLE 1.—*Duration of Jaundice*

Weeks	Cases
1	11
2	16
3	17
4	5
5	6
6	6
7	8
8	10
9	2
10	2
11	1
12	2
15	1
16	3
	90
Uncertain	10
Total	100

In others there were nausea, more malaise and epigastric distress, while in a few cases vomiting was persistent, and there was inability to take much food, with subsequent loss of weight and strength. Itching was relatively infrequent. In some cases the symptoms suggested disease of the gallbladder and in 2 cases the symptoms were progressive and the outcome fatal. The usual dark-colored urine and clay-colored stools were present. The liver was palpable in about one third of the cases. No difference in subjective signs served to aid in the determination of causal factors. Tests of hepatic function were made of hospital bed patients, but these were of no help in separating the cases into groups.

INCIDENCE BY MONTHS

Early in this study it was noted that jaundice appeared in these cases in groups. Table 2 shows the incidence in these cases by months, with 70 to 75 per cent of the total cases grouped. There was an increased incidence from March to June 1930, from December 1930

to March 1931, from December 1931 to March 1932 and in the latter part of 1932. There were two groups in 1933, two in 1934 and a smaller group in 1935. The epidemic of 1930, consisting of 10 cases in four months, was studied. In 8 of these cases one course of arsphenamine and one of a bismuth preparation preceded jaundice. In only 1 of these, a case of latent disease, had a complete series of both drugs been given. In 9 cases the course of bismuth was interrupted by jaundice. Four of these were cases of early secondary disease, and in view of the insufficient treatment the effect of syphilis on the liver would seem the most probable agent in provoking jaundice.

In most cases jaundice appeared in 1933 and 1934, but no reason for this was found. In more cases the disease appeared in the spring, but the grouping by seasons is not particularly striking. As a cause

TABLE 2.—*Incidence by Months*

	1929	1930	1931	1932	1933	1934	1935	Total
January	..	..	2	3	1	2 A	4	12
February	..	..	4	1	1 A-N	..	3	9
March	..	3	1	3	3	4	A	14
April	..	3	..	..	1	3	S	7
May	..	2	..	1	4	3 S	1 N	11
June	..	2	..	2	A	2 N	1	7
July	..	..	..	..	2	3	..	5
August	..	..	..	1	6 N	1 A	2	10
September	..	..	..	1	2 N	N	..	3
October	..	1	..	2	..	..	1 N	4
November	..	..	..	1	1	2 N	3	8
December	1	1	1	3	1	2 A	S	9
Total	1	12	8	18	22	23	15	99

Capitals refer to new lots of arsenicals, A to arsphenamine; N to neoarsphenamine and S to sulfarsphenamine.

for this grouping some change in the arsphenamine was suspected, and in the last three years records were kept of the dates when a change in the lot number of arsphenamine was made. This has been indicated in the table. In 1933 and again in 1934 there was a suggestion of an "epidemic" after a new lot of arsphenamine was introduced. No coincidence was noted with the other arsenicals.

The incidence of jaundice in the medical department of the hospital was also watched. In 1931, 1932, 1933 and 1934 it occurred in 23 cases in the entire outpatient department, while occurring in 71 in the dermatologic department. The incidence was well distributed over the year in 1931. There were only 3 cases in the outpatient department in 1932, occurring in January and December; and there were scattered cases in 1933. The cases in the outpatient department were grouped in February and May in 1934, which was not consistent with the grouping of cases in the dermatologic department. No change in technic was made, and no other factor appeared to account for the

apparent grouping of these cases in a definite period of the year. An epidemic factor appears to be the most probable explanation of the grouping.

BISMUTH THERAPY

The standard course of bismuth therapy consisted of fifteen weekly intramuscular injections of either bismuth subsalicylate or quinine iodobismuthate. The latter preparation was used consistently early in this period and bismuth subsalicylate more in the last two or three years. There were 45 cases in which treatment was begun with a bismuth compound, in 38 with bismuth subsalicylate and in 7 with quinine iodobismuthate.

In 67 cases the jaundice appeared during a series of injections of a bismuth preparation. In 50 per cent of these cases the manifestation appeared between four and ten weeks after the beginning of bismuth therapy and in 33 per cent between four and seven weeks after bismuth medication was started (table 3). Jaundice appeared in 11 cases after part of a series of bismuth medication and one series of arsphenamine, with a minimum of four injections of bismuth preparation and five arsphenamine and a maximum of fifteen of a bismuth compound and ten of arsenic. The arsenical preparations included arsphenamine, neoarsphenamine and tryparsamide. In 25 cases the jaundice appeared after one course of bismuth therapy, one of arsphenamine and part of a second course of bismuth. In these cases the minimum was fifteen injections of a bismuth preparation and ten of arsphenamine, while the maximum was thirty of the bismuth compound and ten of arsphenamine. In 5 cases jaundice appeared after two injections each of a bismuth preparation and arsphenamine and in 3 cases after five courses of treatment, beginning with a course of bismuth medication.

TABLE 3.—*Jaundice in Relation to Bismuth Therapy*

	Number of Injections in Course Before Onset of Jaundice												
	2	3	4	5	6	7	8	9	10	11	12	13	14
Number of cases (67)....	3	5	8	6	6	8	4	5	4	6	4	2	6

In 3 cases only two injections of a bismuth preparation had been given. In 1 of this group no other treatment had been given, and in 1 other a previous course of eleven injections of a bismuth preparation had been given. The patient was a 38 year old man with latent syphilis. It is of interest that this patient had another attack of jaundice later in the same year, after ten injections of arsphenamine and after the third injection of a bismuth preparation. This attack lasted twelve weeks; the first attack had lasted five weeks. No evidence of disease of the gallbladder was found, though two stones were found in one

kidney. In the third case two injections of a bismuth compound following a course of ten injections of arsphenamine preceded the attack. The patient was 21 years old and had late secondary syphilis.

ARSENICAL THERAPY

In view of the fact that many reports refer to arsphenamine jaundice, it is of special interest to investigate carefully the cases in which arsphenamine was used. In 55 cases the first medicament given to a patient was arsenic; in 30, neoarsphenamine; in 21, arsphenamine, and in 4, another preparation. In all but 2 cases some arsphenamine had been given before jaundice appeared, and in 18 cases more than one arsenical preparation had been used.

In 4 cases the jaundice appeared after the use of arsenic alone: in 1 after four injections of arsphenamine; in 1 after sixteen injections of tryparsamide; in 1 after fourteen injections of neoarsphenamine (in two series, one of ten and one of four injections), and in 1 after five injections of neoarsphenamine and nine of tryparsamide. In only 9 cases were less than nine injections of an arsenical preparation administered. The longest series consisted of thirty injections in three periods.

In only 11 cases did jaundice interrupt a course of arsenic while in 67 cases the course of bismuth was interrupted. Of the 11 cases 9 were instances of late or congenital syphilis. One man with the primary lesion had considerable reaction about the lesion and a definite Herxheimer reaction. A person with secondary syphilis had had a series of ten injections of arsphenamine and one of fifteen injections of quinine iodobismuthate before the three injections of arsphenamine which preceded his jaundice by two weeks. There was no evidence of any other reaction than jaundice in any of these cases. In only 5 cases did other manifestations of sensitivity to arsenic develop, such as nitritoid reactions, vomiting, mild dermatitis or a localized Herxheimer reaction.

Tryparsamide was given in 11 cases in which jaundice appeared. In 5 a bismuth preparation had been given alone and in 4 others in addition to a course of another arsenical compound. In only 1 case had tryparsamide been given alone. During this period 9,745 injections of tryparsamide had been given, so that in 1 case in every 886 in which injections of tryparsamide had been given jaundice developed.

In 37 cases jaundice appeared after one course of arsenic and one course, or a portion of a course, of a bismuth preparation. The minimum course preceding jaundice in this group was eight injections of arsphenamine and three of a bismuth compound or five of arsenic and five of a bismuth preparation. The maximum was ten of arsenic and sixteen of a bismuth preparation.

In only 3 cases were more than twenty injections of an arsenical given, one series each of arsphenamine, neoarsphenamine and tryparsamide. In 4 more twenty injections—3 of these of arsphenamine—were given. In 2, only three of neoarsphenamine and two of arsphenamine were given, so that there was considerable variation in the amount of arsenic received by patients in whom jaundice developed, though in 50 per cent of cases nine, ten or eleven injections were given. The amount of arsphenamine injected was certainly not the sole factor, for in many cases far more than this amount was given in the course of antisyphilitic treatment.

Table 4 indicates the number of weeks after the last injection of arsphenamine before jaundice occurred.

In 75 per cent of cases jaundice occurred between four and fourteen weeks after the last injection of arsphenamine, in the greatest number eight or nine weeks after the last dose of arsphenamine. In general,

TABLE 4.—*Occurrence of Jaundice in Relation to Arsenic*

	Weeks After Last Injection of Arsenic																			
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
No. of cases (97)*	4	6	4	2	6	7	4	4	10	13	7	5	6	5	6	2	2	0	1	0	1

* In 1 case jaundice appeared thirty weeks and in another thirty-two weeks after the last injection.

it can be said that if the jaundice is due to the arsphenamine there is a relatively long latent period in which the arsenic exerts an effect on the hepatic cells. Individual patients undoubtedly vary in sensitiveness to arsenic, and there may be a variation in the hepatotoxic effect of the arsenic preparation.

In 14 cases jaundice developed within two weeks after the last injection of arsphenamine. Ten of these were instances of latent disease.

In 9 cases there was no antisyphilitic treatment for at least two months before the jaundice appeared. The longest interval without treatment was four and one-half months, and in only 3 cases did more than three months elapse without treatment. Three patients had only one series of bismuth injections and one of neoarsphenamine before jaundice occurred. Insufficient treatment was probably a factor in these and in a case of primary disease in which three injections of neoarsphenamine, five of arsphenamine and eleven of a bismuth preparation had covered a year.

TWO ATTACKS OF JAUNDICE

Four patients had two attacks of jaundice.

CASE 1.—In a case of latent syphilis in a man aged 38 jaundice had been present for five weeks in 1934, just after two injections of bismuth subsalicylate.

Bismuth therapy was resumed and ten injections of arsphenamine given. After three more treatments with a bismuth compound in the second course his jaundice reappeared and persisted for twelve and one-half weeks. No evidence of organic hepatic disease was found. Renal stones, however, were shown by roentgen examination.

CASE 2.—In a case of secondary syphilis in a man aged 29 jaundice had been present for three weeks just before treatment was started, in December 1933. This may have been real syphilitic hepatitis. Ten injections of arsphenamine were then given, followed by a month's rest and twelve injections of bismuth salicylate. Jaundice occurred one week later and lasted three and one-half weeks. The patient continued under treatment with arsphenamine and a bismuth compound, and no further complication developed.

CASE 3.—A 12 year old girl with congenital syphilis and interstitial keratitis, after eighteen injections of neoarsphenamine and eight of quinine iodobismuthate, had jaundice for three weeks in March 1932. She had two and one-half courses of neoarsphenamine and two of a bismuth compound, and jaundice developed again for five weeks in 1933, after the fifth injection of neoarsphenamine.

CASE 4.—A man aged 24 suffering from primary syphilis had had jaundice at the age of 9 years. A short period of jaundice followed two treatments with arsphenamine during hospitalization. He then had fourteen injections of bismuth subsalicylate and jaundice for a week. He had further treatment with arsphenamine and a bismuth preparation without disturbance.

DEATHS

In 3 cases of jaundice there was a fatal outcome, 2 of acute yellow atrophy and 1 of stricture of the common duct.

CASE 1.—A 55 year old woman with latent syphilis had fifteen injections of a bismuth preparation, ten of neoarsphenamine and fifteen more of a bismuth compound. Jaundice developed five weeks later. The patient died fourteen months after her first treatment. At autopsy subacute yellow atrophy and probable gumma of the liver were seen.

CASE 2.—A woman of 48 with syphilis of the central nervous system had six injections of a bismuth preparation, followed in one month by sixteen of tryparsamide. Jaundice developed one week later, lasting for seven weeks before she died. Atrophic cirrhosis and esophageal varices were observed at autopsy.

CASE 3.—A girl aged 19 with congenital syphilis had had considerable treatment in 1931, 1932 and early 1933. About three weeks after an operation for gallstones jaundice developed; this persisted for three weeks before she died.

CAUSES OF JAUNDICE

Much discussion has arisen over the exact factors which provoke jaundice during antisyphilitic treatment. Table 5 shows the principal theories.

Spirochaeta pallida alone, of course, can produce an inflammatory reaction in the liver of either mild or severe type. This may occur before treatment is started and relatively early in the general invasion

of the body by spirochetes. In an occasional case the disease may progress to icterus gravis, resulting in the acute yellow atrophy so well described by Wile and other authors.

Late syphilis may eventuate in some type of interstitial hepatitis or cirrhosis, with its chronic persistent manifestations, or in localized hepatitis or gumma. In a few cases of long-continued disease amyloid degeneration occurs.

Milian and his followers have been strong advocates of the theory that jaundice is due to a recurrence in the liver comparable to that seen in the nervous system. This type should theoretically appear in cases of inadequate treatment earlier, when the spirochetes, their activity perhaps increased by ineffective therapy, commence a more vigorous attack on the hepatic cells. These observers have pointed out that more arsphenamine aids in clearing up the jaundice and that the jaundice

TABLE 5.—*Causes of Jaundice in the Treatment of Syphilis*

Cause	Stage of Syphilis	Outcome
Syphilis alone	Early: Mild	Hepatitis; cholangitis
	Severe	Acute yellow atrophy
	Late	Gumma; cirrhosis; amyloid degeneration
Arsenic alone	.....	Hepatitis; cholangitis
Syphilis and arsenic	.....	Hepatorecurrence; hepatic Herxheimer reaction
Bismuth, with other factors		
Syphilis, arsenic and infection		
Infection, epidemic jaundice (catarrhal)		
Coincident nonsyphilitic hepatic disease	.....	Cholecystitis; cholelithiasis; pancreatitis, etc.

usually appears six to eight weeks after treatment has been stopped as do neurorecurrences. This theory again may be true of a small group of cases in which jaundice occurs some weeks after a relatively ineffective amount of treatment, especially in cases of secondary disease.

Arsenic has received the blame for jaundice occurring during treatment for many years. Jaundice has been reported following the injection of arsphenamine in nonsyphilitic persons. Much work has been done, notably by Lewin, on the toxic action of arsphenamine preparations on the liver. That action is not surprising when one remembers that there is from 100 to 200 mg. of metallic arsenic in a dose of neoarsphenamine, and that a dose of tryparsamide contains more than this amount. Osborne's microchemical studies on arsenic have indicated its presence in the liver at various times after the injection of different forms of the drug. The toxic effect on hepatic cells is agreed on by most authorities. A group of English observers reported that postmortem examination in cases of fatal outcome after injections of arsphenamine showed histologic details similar to those caused by

trinitrotoluene and suggested that the hepatic changes were due to a direct toxic action. At the same time the possibility that these toxic effects may be the result of specific sensitization of hepatic cells rather than of a destructive chemical action should also be borne in mind.

It can be said, however, that an approximately normal and healthy liver is probably not injured in the great majority of cases by the usual forms of treatment with arsphenamine and its substitutes. On the other hand, Lewin has expressed the belief that in 65 per cent of cases in which arsenical preparations are administered some dysfunction of the liver will result. Sanes and Jordan in November 1935 reported 2 cases of nonfatal jaundice following arsphenamine therapy in which they had had the unusual opportunity of making histologic studies of the liver. One patient died from a bleeding peptic ulcer four weeks after the jaundice had gone, and the other was operated on during jaundice for suspected gallstones, and a biopsy specimen was taken. They stated that the histologic picture in both cases resembled closely that observed in cases of fatal jaundice following injections of arsphenamine, but they agreed that the picture coincided with reported descriptions of lesions in catarrhal jaundice of obscure toxic source. They were unable, therefore, to separate catarrhal jaundice from the postarsphenamine type in these cases.

Much has been written about the joint effect of arsenic and syphilis on the spirochetes and the hepatic cells. In active syphilitic infection a great number of spirochetes are in the liver, and when many of them are killed by the arsphenamine, endotoxins are liberated, and these can well exert a damaging effect on the already congested hepatic cells. Thus, a localized hepatic reaction with resulting jaundice—a Herxheimer reaction—comparable to the reactions often seen on the skin may be present. This is a reasonable explanation for the manifestation in some cases. There were, however, in this series of cases only a few in which jaundice occurred during the course of arsphenamine.

The large number of cases of jaundice in which comparatively few injections of arsphenamine are given, as well as the large number of cases of syphilis in which much more arsphenamine produces no jaundice, would argue against arsphenamine as the main factor. It does not seem probable from a study of these cases that arsphenamine is the only cause, or even the chief cause.

Little has been written concerning the effect of bismuth therapy on the liver, but bismuth in the presence of certain fresh organ extracts produces a new bismuth compound, which Levaditi called bismoxyl. Thus fresh liver extract, by reason of its activating agent in combination with certain bismuth compounds, has been found to have a much more powerful effect in experimental work when combined with bismuth than when used alone. The way in which these tissue extracts act is not

known, but a definite increase in therapeutic power in association with bismuth compounds has been demonstrated. With such an effect shown, it is reasonable to suppose that under exceptional conditions an increased effect on hepatic cells could be produced, perhaps directly or by the destruction of foci of spirochetes quickly in relatively large numbers.

While hepatic lesions have been shown experimentally to follow bismuth medication, it is known that patients with secondary syphilis in whom jaundice develops after arsphenamine therapy can be treated safely with bismuth preparations, and numerous cases have been reported of the efficacy of the drug in syphilitic jaundice.

The occurrence of jaundice in so many cases in this series in which bismuth compounds were used brings up the question of bismuth as a partial cause. If the bismuth is activated by liver extract and some slight damage is done by arsphenamine, or by syphilis or by both, the bismuth may be the last straw in breaking down certain of the hepatic functions and producing jaundice.

An infectious factor causing epidemic jaundice—perhaps called catarrhal jaundice—has received much serious consideration in the effort to explain jaundice in this group of cases. Numerous reports of mild and severe epidemics of jaundice in nonsyphilitic persons have been made, especially in the younger age groups. Stokes called attention to the marked increase of jaundice from 1918 to 1920, over the previous two year period, with no change in the technic or the brand of drugs used. He stated that in many cases there are a distinctive prodrome, and a typical course, that the process is hemolytic and that it is possible to continue administration of neoarsphenamine through the course of jaundice without difficulty. The general increase in the incidence of the disease since the World War has been commented on. Figures for the German Navy for 1910 to 1929 showed a striking parallelism between the number of cases of postarsphenamine and of catarrhal jaundice.

Opie's work with chloroform indicated that the administration of chloroform and the injection of living bacteria made more serious changes in the hepatic cells than did the use of chloroform alone. If there is an analogy on this point between arsenic and chloroform, the arsphenamine could be the predisposing factor in causing damage to hepatic cells, and the picture could be completed by a low grade infection. Catarrhal jaundice, so called, is not unusual, and most observers have given increasing attention to this condition, at least as one factor in the production of the type of jaundice under consideration.

Coincidental hepatic disturbance must always be ruled out as a possible factor. The causes of obstructive jaundice are many, and the most important at least should be carefully reviewed in any case under observation in which jaundice develops, no matter what the amount of

treatment has been or how long an interval has elapsed between courses of treatment. In this series at least 3 cases should be classified as instances of this type.

The effect of multiple factors is difficult to estimate, but it seems clear that more than one causal agent is at work, at least as far as the analysis can be carried at present. Neither arsenic nor syphilis can account for the jaundice in all cases, or even in a large majority, although much is known concerning the action of these agents on the liver. The grouping suggests an epidemic factor. The number of cases appearing during a series of injections of bismuth preparation raises the question of bismuth as a factor in addition to those mentioned. In the days when mercury was used, it was considered a factor in jaundice, perhaps through its action on the kidneys. Bismuth has a far less deleterious effect as a rule, but as a heavy metal may add its quota to the damage already produced.

The effect of alcohol or of some mild hepatic disease, with subsequent alteration of function, cannot be measured at the present time, but either may play a minor part in the production of the syndrome of jaundice.

DIAGNOSIS

In the differential diagnosis of these conditions, little progress has been made, especially in differentiating catarrhal jaundice and jaundice due to arsenic. Wile has called attention to the difference in symptoms and emphasized the need of careful study of the history, but I have not been helped much by the patients' symptoms. The tests of hepatic function, of which much had been hoped, indicate the functional disturbance and estimate the amount of damage but have not as yet aided in establishing the causal factor. Some of these tests, if done routinely, would have a preventive value, in avoiding further treatment after any abnormal change is shown by the test. It is, however, impractical at the present time to make these tests a routine procedure. The Herxheimer reaction and the hepatorecurrences after a lapse in treatment can be detected, but it is difficult to state how late an effect of arsphenamine can appear after its administration. It must be remembered that the catarrhal, and perhaps arsenical, jaundice may produce symptoms suggesting gallstone or some other type of obstructive jaundice. It has been a disappointment in reviewing these cases not to be able to set up more definite criteria for grouping them. The study has, nevertheless, emphasized rather clearly the possibilities of accumulative damage done by the several factors considered.

TREATMENT

In the treatment of this form of jaundice I have tried to put the patient in bed and under observation. In general, administration of saline laxatives, forcing of liquids and a high carbohydrate and low fat

diet have been prescribed. Intravenous injection of sodium thiosulfate has not proved its worth. Intravenous use of calcium preparations—either 10 per cent calcium gluconate or the calcium thiosulfate reported by Schamberg—may be of help. Intravenous administration of dextrose has been tried in more cases recently. In regard to the continuation of antisyphilitic treatment, the French school headed by Milian has expressed belief in the continuance of such treatment, but in my opinion the more conservative point of view is best. In the early stages of syphilis or in the presence of active syphilitic lesions the use of arsphenamine, perhaps in slightly less than the usual dose, of a bismuth preparation and perhaps of potassium iodide is justified. The question is difficult to decide, and the picture in the individual case must be the guide. In cases of late and of inactive congenital disease the active treatment should be omitted until the jaundice has disappeared for several weeks and then resumed, perhaps with a bismuth compound at first. In the cases in which jaundice appears some time after treatment has been stopped it is well to suspect hepatorecurrence and to treat the patient with a bismuth compound or mercury and iodide rather than arsenic at this time. It will be of interest to follow these cases for some years, as it has been reported (O'Leary) that occasionally a patient who has had jaundice returns some time afterward with cirrhosis. Further study of more cases is necessary for determination of the final outcome.

SUMMARY AND CONCLUSIONS

One hundred (100) cases of jaundice occurring in the course of antisyphilitic treatment have been reviewed.

Syphilis alone seems a relatively rare causative factor.

Arsenic alone, except in cases of sensitivity to arsenic or of variance in the hepatotoxicity of the preparation, does not account for the disease in many cases. One cannot escape the impression, however, that it has some effect in the majority of cases.

An epidemic factor is suggested by the grouping of cases over a period of six years.

Bismuth, with treatment in 60 per cent of cases in this series interrupted by jaundice during the course of bismuth medication, appears to participate to a greater degree than is usually accepted.

Three cases of two attacks of jaundice are reported.

Eleven cases in which jaundice occurred during tryparsamide treatment are mentioned.

Three deaths occurred, 2 from cirrhosis.

Bismuth and arsenical therapy in conjunction with some mild infection can exaggerate the damage inflicted by Spirochaeta pallida on hepatic cells and produce jaundice as a complication of therapy.

ABSTRACT OF DISCUSSION

DR. PAUL A. O'LEARY, Rochester, Minn.: Twelve or fifteen years ago I observed a great many patients in whom jaundice developed after antisyphilitic treatment. During the past five years I have encountered practically no such cases. Aside from the use of slightly smaller doses of old arsphenamine, the drugs, technic and time of administration have remained unchanged. I believe that a discussion of postarsphenamine jaundice would be incomplete if one failed to mention the fact that jaundice which appears in a patient who has received treatment for syphilis may be in no way related to the syphilis or to the treatment. Extrahepatic factors, such as stones and cancer, must be borne in mind, as well as arsenic, syphilis or some other infectious agent, as the cause of the icterus. I have on file the records of 10 patients who have died of cirrhosis of the liver, all of whom had some years previously had "postarsphenamine jaundice." Four of these patients had an asymptomatic type of cirrhosis, by which I mean that the hepatic atrophy had not progressed to the point where it produced clinical evidence of hepatic dysfunction. However, the 4 patients died unexpectedly of ruptured esophageal varices.

I do not believe that Dr. Lane should be chagrined over the fact that he has not been able to determine which of the numerous factors caused the jaundice, because the influence of arsenic, syphilis, alcohol and infection, either alone or in combination, must be considered in each case.

DR. UDO J. WILE, Ann Arbor, Mich.: The members will no doubt recall that in Chicago in 1933 I presented a study (Wile, U. J., and Sams, W. M.: Study of Jaundice in Syphilis; Its Relation to Therapy, *Am. J. M. Sc.* **187**:297-315 [March] 1934) of almost the same number of cases of jaundice occurring in association with syphilis over a period of many years. A careful analysis of the results showed that arsenic was definitely the responsible factor. It may perhaps be pointed out that in incriminating bismuth Dr. Lane has shown this drug alone to have been used in a very few cases and that in some of the others he has incriminated bismuth on the basis of the jaundice having occurred after bismuth medication. Arsenic was known as a hepatotoxic drug, capable of causing jaundice, long before it was used in the treatment of syphilis. The heavy metals are generally considered nephrotoxic. However, if it can be shown (and I believe it may) that bismuth as well as arsenic is hepatotoxic, this fact is another commentary on the limitations of the use of protoplasmic poisons in antisyphilitic treatment.

DR. NORMAN N. EPSTEIN, San Francisco: In a study of the hepatic complications occurring in patients in the syphilis clinic some three or four years ago, certain points seemed evident, and I believe they are of some interest.

First, hepatic complications are seen much more commonly in the syphilis clinic than in the medical clinic. This is undoubtedly due to the fact that several factors are present which contribute to injury of the liver. Syphilis itself not uncommonly affects the liver, and arsenic is hepatotoxic. The status of the patient as to alcohol and focal infection must also be considered.

Secondly, I was much interested in attempting to determine whether patients entering the syphilis clinic had previous hepatic damage which could not be determined by physical examination, that is, latent hepatic disease. The patient with latent hepatic disease is more likely to suffer injury from drugs than the one who has a normal liver. Of 153 patients, there were 26 who did not present normal findings on tests of hepatic function. Twenty others showed definite evidence of hepatic damage. From a practical standpoint the following problem

presents itself. A patient enters the clinic, and jaundice develops during treatment. Is one to treat that patient again with arsenic, or should treatment be limited to administration of a heavy metal? I think that this whole question depends on whether the liver returns to normal, not only from the standpoint of the clearing of the jaundice but also from that of a thorough study of the hepatic function. In the young adult with early syphilis who has jaundice it is unusual for a second attack of jaundice to occur if treatment is continued. In the age group between 40 and 60, however, one finds that residual damage is common, and the continuation of arsenic therapy becomes hazardous.

DR. EARL D. OSBORNE, Buffalo: I believe that physicians are inclined to place too much importance on the bismuth or arsenic radical, forgetting all about the remainder of the complex organic molecule. As a matter of fact, the same type of jaundice has occurred after the use of many organic chemicals without the bismuth or arsenic. The thing that is common to all such drugs is the benzene ring. It does not appear to make any difference whether there are one or two benzene rings. Mapharsen, for instance, containing one benzene ring in its molecule, has a definite index of hepatic toxicity. In view of the tremendous amounts of inorganic arsenic and bismuth which can be consumed without hepatic damage, it seems to me that the remainder of the molecule, particularly the benzene ring, is of the greatest importance in the production of hepatitis.

DR. RUBEN NOMLAND, Iowa City: Dr. Lane emphasized the importance of bismuth as a factor in therapeutic jaundice. My associates and I (Nomland, R.; Skolnik, E. A., and McLellan, L. L.: Jaundice from Bismuth Compounds Used in the Therapy of Syphilis, *J. A. M. A.* **111**:19 [July 2] 1938) recently finished the study of a series of 75 cases of jaundice occurring at the Rush Medical College over a period of five years.

We felt that the condition in 32 of the cases included in this study was caused by bismuth. Of these 32, neoarsphenamine had been given more than three months previous to the onset of the jaundice in 22, but bismuth was the main factor, and this will probably answer Dr. Wile's question. Of the same 32, no neoarsphenamine or other arsphenamine was given at any time in 10, and in practically every case jaundice developed within three weeks of the latest injection of a bismuth compound. It seems, therefore, that bismuth is capable of causing therapeutic jaundice which is indistinguishable from neoarsphenamine jaundice. When both bismuth and neoarsphenamine were given and the jaundice occurred ninety days after the last dose of neoarsphenamine, we felt that the neoarsphenamine should not be considered a major factor. I realize that the so-called delayed neoarsphenamine jaundice is an acceptable clinical concept, but I still feel that if the jaundice develops much later than twelve weeks after the last dose of neoarsphenamine one should think twice before ascribing it to the drug. However, one seventh of our patients with therapeutic jaundice had received bismuth alone.

DR. SAMUEL SWEITZER, Minneapolis: I should like to ask Dr. Lane the total number of cases of syphilis from which he reported the 100 cases of jaundice. I observe about 400 new cases of syphilis a year and I can't remember that I have had a case of jaundice.

DR. C. GUY LANE, Boston: In answer to Dr. Sweitzer's question, I stated that these 100 cases of jaundice occurred in approximately 3,100 cases of syphilis; so the incidence was about 3 per cent. In general, I believe fewer cases of jaundice have been observed in the last two years than before. I have kept up my interest more in the cases which I saw in this group than I have in the more

recent ones, but I do know that there are still a few cases appearing. There will be an interval without any, and then there will be a series of 2, 3 or 4 in a relatively short period. A statement by Dr. O'Leary some time ago indicates the occurrence of fatalities following years after jaundice, and my associates and I have been on the watch for fatalities occurring in this group particularly, but so far we have not found any of the late fatal cases in our series. I have been watching particularly these 4 patients who have had two attacks, but so far they are still alive.

It has been my feeling that the bismuth has not been an important factor but that it has been a further burden—a further insult perhaps—in addition to the insult given by arsphenamine, by the action of the spirochetes and by a possible epidemic factor which, of course, cannot be escaped when cases have occurred so well grouped as they have at our clinic.

QUANTITATIVE INVESTIGATION OF PORPHYRIN METABOLISM IN DISEASES OF THE SKIN

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The dermatologist's interest in porphyrin metabolism has been concerned mainly with abnormal formation and excretion of porphyrin in rare cases of chronic or congenital sensitivity to light.[1] It was first thought that hematoporphyrin was the porphyrin which accounted for the clinical symptoms of hydroa aestivale, as it could be shown that hematoporphyrin was possessed of photosensitizing powers when injected experimentally into animals [2] and into human beings.[3] Later Fischer [4] proved that hematoporphyrin, which is readily prepared in the laboratory from blood, does not appear to play any important role in porphyrin metabolism in nature. In a long series of investigations in the case of congenital porphyria of Petry, Fischer was able to show that the excreted porphyrins differed fundamentally from hematoporphyrin in the melting point of the esters and in a greater number of carboxyl groups in the molecule. These porphyrins were labeled uroporphyrin and coproporphyrin. Coproporphyrin, which is formed in small amounts in the body and is normally excreted in bile, urine and feces, has only a slight photosensitizing effect when injected experimentally into animals.[5]

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1. Günther, H.: Die Hämatoporphyrie, Deutsches Arch. f. klin. Med. **105**: 89-146 (Dec. 20) 1911.

2. Hausmann, W.: Die sensibilisierende Wirkung des Hämatoporphyrins, Biochem. Ztschr. **30**:276-316, 1911.

3. Meyer-Betz, F.: Untersuchungen über die biologische (photodynamische) Wirkung des Hämatoporphyrins und anderer Derivate des Blut- und Gallenfarbstoffs, Deutsches Arch. f. klin. Med. **112**:476-503, 1913.

4. Fischer, H.: Ueber das Urinporphyrin, Ztschr. f. physiol. Chem. **95**: 34-60 (Aug. 12) 1915; Ueber das Kotporphyrin, ibid. **96**:148-182 (Dec. 8) 1915.

5. Kämmerer, H., and Weisbecker, H.: Ueber die sensibilisierende Wirkung der Porphyrine, besonders des Fäulnisporphyrins, gegenüber Licht- und Röntgenstrahlen, Arch. f. exper. Path. u. Pharmakol. **111**:263-280, 1926.

Uroporphyrin has a stronger photosensitizing effect on the skin, but except in pathologic conditions, it is formed only in negligible amounts or not at all. Other porphyrins, such as protoporphyrin, mesoporphyrin and deuteroporphyrin, have been found in human feces in relatively large amounts after bacterial action on certain foodstuffs which contain the hemin complex, such as blood or meat.[6]

Uroporphyrin is the only porphyrin in the body which is insoluble in acidified ether. It is excreted abundantly in such rare metabolic disorders [6a] as acute porphyria with symptoms of gastrointestinal or nervous disease and in congenital diseases of the skin, such as epidermolysis bullosa and hydroa vacciniforme. The presence of uroporphyrin in the urine in these diseases establishes the existence of porphyria, but it does not follow that the increased formation and excretion of the porphyrins produce the hypersensitivity to light. In a recent admirable survey, Turner and Obermayer [7] reviewed the literature in this regard and reported an experimental study of a case of epidermolysis bullosa with porphyria in which they were unable to demonstrate evidence of sensitivity to light. Blum and Pace [8] experienced the same failure in studying hydroa vacciniforme with porphyria. In fact, in more than half of the reported cases of hydroa vacciniforme, investigations gave no evidence of porphyria. In some cases of porphyria associated with sensitivity to light it has been possible to show an exaggerated reaction of the skin to small doses of ultraviolet or visible rays, but in no instance has it been possible to provoke the typical lesions of hydroa vacciniforme by such exposure.[9] Urbach [10] recently found increased porphyrins in the feces but not in the urine in certain cases of light-sensitive dermatoses associated with reduced hepatic function and an overgrowth of pathogenic organisms in the feces.

In other conditions showing clinical evidence of hypersensitivity to light, such as pellagra and disseminated lupus erythematosus, porphyria is of uncertain occurrence. Beckh, Ellinger and Spies [11] found

6. Kämmerer, H.: Ueber Porphyrinbildung durch Darmbakterien, Klin. Wchnschr. **2**:1153-1155 (June 18) 1923.

6a. Waldenström, J.: Studien über Porphyrie, Acta med. Scandinav. (supp.) **82**:3-254, 1937.

7. Turner, W. J., and Obermayer, M. E.: Studies on Porphyria: II. A Case of Porphyria Accompanied with Epidermolysis Bullosa, Hypertrichosis and Melanosis, Arch. Dermat. & Syph. **37**:549-572 (April) 1938.

8. Blum, H. F., and Pace, N.: Studies of Photosensitization by Porphyrins, Brit. J. Dermat. **49**:465-485 (Nov.) 1937.

9. Carrié, C.: Die Porphyrine, Leipzig, Georg Thieme, 1936, pp. 67-69.

10. Urbach, E.: Schwerste Lichtdermatosen auf Grundlage von isolierter pathologischer Porphyrinbildung im Darme infolge Dysbakterie und Hepatopathie, Klin. Wchnschr. **17**:304-310 (Feb. 26) 1938.

11. Beckh, W.; Ellinger, P., and Spies, T. D.: Porphyrinuria in Pellagra, Quart. J. Med. **6**:305-319 (July) 1937.

increased coproporphyrinuria in 14 cases of alcoholic pellagra, but it is well known that chronic alcoholism in itself is accompanied with increased excretion of porphyrins.[12] However, Ellinger and Dojmi[13] had previously observed increased porphyrinuria in 8 cases of active endemic nonalcoholic pellagra in Jugoslavia. Massa[14] observed abnormal porphyrinuria in 2 cases of pellagra and in cases of dermatoses associated with sensitivity to light. The recent report by Ludy and Corson[15] of hematoporphyria in connection with acute lupus erythematosus is of considerable interest; details of the technic of the investigations were not given, however, and in view of the present knowledge of the subject it seems improbable that the porphyrins were excreted as hematoporphyrin. To summarize the opinions in regard to the relation of sensitivity to light to porphyria,[16] it may be said that whereas the two conditions may appear at the same time in the same person, there is not sufficient evidence to show that the one condition is directly dependent on the other.

Aside from sensitivity to light, however, it is recognized that abnormal metabolism of porphyrin is associated with disorders of the general health in which the skin may play a part. There is, first of all, an appreciable daily excretion of endogenous porphyrins by normal persons, in amounts of 200 to 500 micrograms (0.2 to 0.5 mg.), of which no more than 40 or 50 micrograms appears in the urine.[17] When meat is eaten, as in the ordinary diet, these values may be doubled. The most significant end product of normal porphyrin metabolism is coproporphyrin, and this is excreted in the bile, feces and urine. Damage to the kidneys or bacterial infection of the urinary tract frequently interferes with the demonstration of porphyrins in the urine. The excretion of porphyrins in abnormally large quantities occurs in primary or congenital porphyria and as a significant secondary effect in diseases of the liver, the bone marrow and the reticuloendothelial system. Poisoning by alcohol, lead or other heavy metals and drugs, such as cinchophen and thiosinamine, causes an increased excretion of

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12. Brugsch, J. T.: Toxic Porphyrinuria Following Chronic Alcoholism, Proc. Staff Meet., Mayo Clin. **12**:609-612 (Sept. 29) 1937.

13. Ellinger, P., and Dojmi, L., cited by Beckh, Ellinger and Spies.[11]

14. Massa, cited by Carrié.[9]

15. Ludy, J. B., and Corson, E. F.: Lupus Erythematosus: Increased Incidence, Hematoporphyrinuria and Spectroscopic Findings, Arch. Dermat. & Syph. **37**:403-416 (March) 1938.

16. Turner and Obermayer.[7] Blum and Pace.[8] Carrié.[9]

17. Brugsch, J.: Untersuchungen des quantitativen Porphyrinstoffwechsels beim gesunden und kranken Menschen: VI. Schlafmittelwirkung und Porphyrinstoffwechsel (Nach Untersuchungen an Geisteskranken), Ztschr. f. d. ges. exper. Med. **99**:585-596, 1936.

porphyrins in normal persons. Reactions of sensitivity to neoarsphenamine and to relatively small amounts of lipoid-soluble hypnotics, such as sulfonmethane, chloral hydrate and chloroform, likewise may cause the excretion of large amounts of porphyrin.[18]

We cannot consider here the question of which isomer of porphyrin is excreted in the cases that are of particular dermatologic interest. It should be mentioned that uroporphyrin and coproporphyrin appear in nature as the I or the III isomer, depending on the relation of the various side chains of the molecule to each other.[19] In endogenous porphyrin metabolism under normal conditions and also in many pathologic conditions the type I isomer is most frequently produced. The type III isomer is directly related to the hemin of hemoglobin, myoglobin or cytochrome or even to chlorophyll, and the isomer III of porphyrin may originate by the decomposition of such pigments in the body. Porphyrins of type I cannot give rise to type III, and vice versa.

Determinations of porphyrin have been made in a considerable variety of pathologic conditions,[20] a few of which may be emphasized because they are of dermatologic interest. Schreus and Carrie[20c] observed increased excretion of porphyrins in association with the administration of the arsphenamines and investigated the relation between fever and porphyrinuria. Scolari[21] found a slight increase in porphyrinuria in cases of psoriasis and eczema and a more pronounced excretion in cases of erythroderma. The effect of variation in diet was not appreciable. Exposure of the skin to heat or to ultraviolet radiation did not enhance the output of porphyrins. Hübner[22] reported increased porphyrinuria in 8 of 33 cases of erythema

18. Brugsch, J.: Die sekundären Störungen des Porphyrinstoffwechsels, Ergebn. d. inn. Med. u. Kinderh. **51**:86-124, 1936.

19. Fischer, H.: Neuere Methoden der Isolierung und des Nachweises von Porphyrinen, in Abderhalden, E.: Handbuch der biologischen Arbeitsmethoden, Berlin, Urban & Schwarzenberg, 1936, vol. 1, pp. 169-216.

20. (*a*) Kämmerer, H.: Biologie und Klinik der Porphyrine, Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong. 45, 1933, pp. 28-60. (*b*) Duesberg, R.: Ueber die Anämien: I. Porphyrie und Erythropoese, Arch. f. exper. Path. u. Pharmakol. **162**:249-279, 1931; II. Anämien und Leberstoff, ibid. **162**:280-295, 1931. (*c*) Schreus, H. T., and Carrié, C.: Weitere Mitteilung zur quantitativen Porphyrinbestimmung im Harn, Klin. Wchnschr. **12**:146-148 (Jan.) 1933; Zur Physiologie und Pathophysiologie der Porphyrin-Ausscheidung, ibid. **12**:745-748 (May 13) 1933. (*d*) Günther.[1] (*e*) Brugsch.[18]

21. Scolari, E.: Alterazioni del metabolismi coproporfirinico in dermatologia e richerche sperimentali sul loromeccanismo, Gior. ital. di dermat. e sif. **76**:1183-1238 (Oct.) 1935; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **54**:397-398, 1936.

22. Hübner, K. H.: Erythema exsudativum multiforme und Porphyrinurie, Arch. f. Dermat. u. Syph. **174**:38-45 (April 8) 1936.

multiforme of the exudative type. Kren [23] mentioned porphyrinuria in cases of pemphigus. Marquardt [24] found great elevation of the rate of excretion of porphyrins in cases of arsphenamine dermatitis and less pronounced but, nevertheless, abnormal values in cases of severe furunculosis and urticaria and in some cases of eczema. He found that relapse in such conditions was heralded by increased porphyrinuria. Before we report our quantitative measurements of porphyrins in assorted dermatologic conditions, the technic of the procedure will be briefly outlined.

METHODS

All the procedures for extraction of porphyrins useful for quantitative purposes rest on the prinicple of Saillet [25] and of Fischer,[19] by which the ether-soluble porphyrins are taken up in ether in the presence of glacial acetic acid. The acetic acid is washed out of the ether with distilled water until the mixture is neutral to litmus, and then the porphyrins are extracted by repeated shaking with small quantities of dilute hydrochloric acid.

It is a characteristic property of porphyrins to fluoresce in ultraviolet light. The measurement of the intensity of the red fluorescence affords a method for the quantitative determination of minute amounts of porphyrins which is actually more sensitive than any simple colorimetric procedure or even than a careful measurement of the bands in the absorption spectrums. The measurement itself may be made by comparison with standard solutions of porphyrin. In the studies at the clinic we have used coproporphyrin [26] as the standard solution, the most useful concentrations being 0.2, 0.1 and 0.05 microgram of porphyrin per cubic centimeter. Comparison can be made directly in quartz or reagent glass vessels of the same diameter, the tubes having no fluorescence of their own. Fluorescence is produced by the light from a quartz mercury vapor lamp which has passed through filters to cut out all radiation of a wavelength longer than approximately 4,000 angstrom units. Examinations are made in a dark room after the eyes have become adapted to the dark for a minimal period of three minutes.

These procedures of extraction and fluorometric comparison have been applied to the quantitative measurement of ether-soluble porphy-

23. Kren, O.: Hautschädidung durch Porphyrin (Cirrhosis hepatis), Dermat. Wchnschr. **102**:602-603 (May 2) 1936.

24. Marquardt: Porphyrinbestimmung im Urin und ihre Bedeutung bei Hauterkrankungen, Zentralbl. f. Haut- u. Geschlechtskr. **53**:525-526, 1936.

25. Saillet: De l'urospectrine (ou urohématoporphyrine normale) et de sa transformation en hémochromogène sans fer, Rev. de méd., Paris **16**:542-552, 1896.

26. Dr. Hans Fischer supplied the pure coproporphyrin used in our experiments.

rins in biologic materials [27] such as urine, feces and bile. The technic for extraction of ether-soluble porphyrins from urine will be given in detail.

Extraction of Ether-Soluble Porphyrins from Urine for Quantitative Analysis.[28]—Samples to be analyzed should be protected from strong light and from bacterial action. Fresh urine is collected in dark brown bottles in which small amounts of toluene have been placed. In the procedure of extraction, violent shaking is to be avoided. Shaking may be done by hand with a rotary motion in a separatory funnel, but if more than occasional analyses are to be made a mechanical rotator is almost indispensable. In such a rotator the speed should be from forty to sixty revolutions per minute. The bottles must be mounted on the shaft of the rotator in an angular fashion, and the bottles should be a third to a fourth full when prepared for extraction. Rubber stoppers may be used, but they should be thoroughly cleansed with dilute hydrochloric acid and rinsed with distilled water before use.

To 25 cc. of urine 10 cc. of glacial acetic acid and 100 cc. of ethyl ether are added. The mixture is agitated by hand in a separatory funnel for forty-five minutes or on the rotator in a stoppered bottle for four hours. The ether extract is then separated, 80 cc. of fresh ether added to the urine and agitation continued for ten minutes by hand or for thirty minutes on the rotator for a second extraction. The two ether extracts are combined and washed with distilled water until the wash water is neutral to blue litmus paper. The ether extract is then agitated by hand in a separatory funnel, with successive portions of 5 cc. of 5 per cent hydrochloric acid until the hydrochloric acid fails to show red fluorescence in ultraviolet light. Fifteen minutes' shaking by hand or thirty minutes on the rotator should suffice for these extractions. In general, two extractions with hydrochloric acid are sufficient to pick up all the porphyrins, and in many cases the total porphyrin fluorescence of urine may then be measured directly.

Final purification of the porphyrin mixtures to rid them of the disturbing effects of urobilin (urine) or chlorophyll derivatives (feces) requires transfer to ether and back again to 5 per cent hydrochloric acid. This is accomplished as follows: Pure solid sodium acetate is added to the 5 per cent hydrochloric acid solution of porphyrins until congo red paper no longer turns blue. From 30 to 50 cc. of ether and 1 or 2 cc. of glacial acetic acid are added and the mixture agitated for a few minutes. The ether layer is separated off and the extraction repeated with successive lots of acetic acid–ether until the aqueous solution no longer shows red fluorescence in ultraviolet light. The combined ether extracts are washed briefly with distilled water (to the first wash water a little sodium carbonate is added) and then are extracted with 5 per cent hydrochloric acid as

27. Fikentscher, R.: Quantitative Porphyrin-Bestimmung durch Lumineszenzintensitätsmessung mit dem Stufenphotometer, Biochem. Ztschr. **249**:257-269, 1932. van den Bergh, A. A. H.; Grotepass, W., and Revers, F. E.: Beitrag über das Porphyrin in Blut und Galle, Klin. Wchnschr. **11**:1534-1536 (Sept. 10) 1932. Brugsch, J. T.: Untersuchungen des quantitativen Porphyrinstoffwechsels beim gesunden und kranken Menschen, Ztschr. f. d. ges. exper. Med. **95**:471-481, 1935.

28. Brugsch, J. T., and Keys, A.: Studies on Quantitative Separation and Estimation of Porphyrins in Minute Amounts: I. Pure Solutions of Single Porphyrins and Synthetic Mixtures of Porphyrins, J. Biol. Chem., to be published.

before. The combined 5 per cent hydrochloric acid extracts now contain the ether-soluble porphyrins of the urine (almost all coproporphyrin) in a relatively high state of purification. In certain rare clinical conditions, such as congenital or primary porphyria, the ether-insoluble uroporphyrin appears in the excreta in considerable amounts. The urine in such cases usually becomes dark on standing. In acid reaction (a few drops of acetic acid is added) primary fluorescence is shown in ultraviolet rays; also the urine after extraction with acetic ether still fluoresces strongly. Examination of the acid urine with a pocket spectroscope will show typical absorption bands if uroporphyrin is present: one broad band in the green and a narrow band between the orange and the red.

Quantitative separation of isomers I and III of the porphyrins is not yet possible. Their recognition depends on the study of the characteristic bands in the absorption spectrums and on the determination of the melting points of the crystallized methyl esters of the respective isomers.

CLINICAL OBSERVATIONS

The level of excretion of coproporphyrin (ether-soluble porphyrin) is not elevated in the most common cutaneous diseases unless there is disturbance of the general health. In no instance was uroporphyrin demonstrated; however, cases of congenital porphyria, hydroa aestivale or epidermolysis bullosa were not among this series of observations. Porphyrins in the feces were analyzed in selected cases but not in all instances. It was found that the fecal porphyrins were elevated in cases of exfoliative dermatitis caused by neoarsphenamine and in 1 case of pityriasis rosea, although in the latter condition porphyrinuria was not present (table 1).

Psoriasis and the Eczema Group.—Among 20 cases of psoriasis normal values for excreted porphyrins were found in all but a few instances in which there were abnormal values in response to treatment. This was found to be true for a large group of cases of eczema, dermatitis venenata, infantile eczema, urticaria, senile pruritus, ichthyosis and atopic dermatitis or neurodermatitis of the localized and disseminated types. There were included 3 cases of exfoliative psoriasis and 1 case of exfoliative dermatitis of uncertain origin (table 2).

Pityriasis Rosea, Lichen Planus and Dermatitis Medicamentosa.—Normal values for excreted porphyrins were associated with these conditions except in certain cases in which there was a reaction of sensitivity to certain drugs (sulfanilamide in 2 instances and neoarsphenamine in 4 instances). Elevated porphyrin excretion has been reported in cases of syphilis after treatment with the arsphenamines,[20c] but we found normal values in such cases, including 2 instances in which there was urticarial evidence of hypersensitivity of the skin after injections of arsphenamine in the treatment of secondary syphilis.

Pemphigus, Erythema Multiforme and Dermatitis Herpetiformis.—In 1 case of pemphigus foliaceus, in contrast with pemphigus vulgaris,

TABLE 1.—*Cutaneous Diseases in Which Porphyrinuria was Normal (Less Than 100 Micrograms of Coproporphyrin in Twenty-Four Hours)*

Disease	Cases	Specimens of Urine Examined
Psoriasis	15	69
Eczema, Neurodermatitis, Urticaria, Pruritus senilis, Ichthyosis	52	233
Pityriasis rosea	3	4*
Lichen planus	3	6
Dermatitis herpetiformis	2	2
Pemphigus foliaceus	1	5
Mycosis fungoides	2	29
Latent syphilis	9	12
Secondary syphilis (after mild arsphenamine reaction)	2	4
Dermatomyositis	2	3
Chancroid	1	2
Urticaria solaris, Eczema solare	9	14
Pellagra	2	2
Lupus erythematosus		
Discoid	4	4
Disseminate	2	11
Dermatitis medicamentosa		
Phenobarbital	1	3
Sulfanilamide	6	13

*Fecal porphyrins, 3,320 micrograms in twenty-four hours in 1 case.

TABLE 2.—*Cutaneous Diseases Associated with Elevated Porphyrinuria (More Than 100 Micrograms in Twenty-Four Hours)*

Disease	Cases	24 Hour Samples: Porphyrin Total	24 Hour Samples: Porphyrin High	Peak Coproporphyrinuria (Micrograms in 24 Hours)	Associated Factors
Psoriasis	4	76	12	315.8	Autoserum given intramuscularly
	1	7	3	348.0	Typhoid vaccine given intravenously
Eczema	6	45	8	175.0	
	1	6	2	167.0	Whole blood given intramuscularly, boiled milk intramuscularly
Dermatitis herpetiformis	1	3	1	117.0	Paravertebral roentgenologic treatment
Lupus erythematosus (discoid)	1	1	1	179.5	Reaction to gold treatment
Dermatitis medicamentosa (sulfanilamide)	2	5	2	141.5	
Eczema solare	2	4	2	159.0	
Dermatomyositis	1	19	1	165.1	
Multiple abscesses	3	22	9	348.2	Occasional fever (1 case)
Extensive burns	1	5	5	121.8	
	1	21	12	237.4	Blood transfusions, fever
Pyoderma gangraenosum with colitis	1	24	23	558.0	Fever
Tuberculosis					
Erythema induratum	1	2	2	299.9	
Scrofuloderma	2	6	3	348.2	
Erythroderma					
Hodgkin's disease	3	20	8	229.3	Fever (1 case)
Leukaemia cutis	2	2	2	148.8	
Erythema multiforme exsudativum	1	3	2	178.1	
Pemphigus vulgaris	2	8	6	257.6	
Neoarsphenamine exfoliative dermatitis	1	5	4	199.2*	
	1	24	4	340.0†	
	1	7	5	628.3	
	1§	29	24	684.0	

* Fecal coproporphyrin, 1,328 micrograms in twenty-four hours.
† Only first four specimens abnormal.
§ Treatment given for nonsyphilitic uveitis.

there was no evidence of abnormal excretion of porphyrin. In 2 cases of extensive pemphigus vulgaris the urine showed excessive amounts of porphyrin independent of the degree of fever that was present intermittently. In 1 case of erythema multiforme of the bullous type there was abnormal excretion of porphyrin, in agreement with the findings of Hübner [22] in a study of this condition. Dermatitis herpetiformis was not associated with alterations from normal except to a slight degree in 1 instance; the patient was being subjected to systemic exposures of filtered roentgen rays.

Lymphoblastoma.—Two patients who had mycosis fungoides in the tumor stage were subjected to repeated examinations for porphyrins, but normal values were obtained in every instance (chart 1). On the

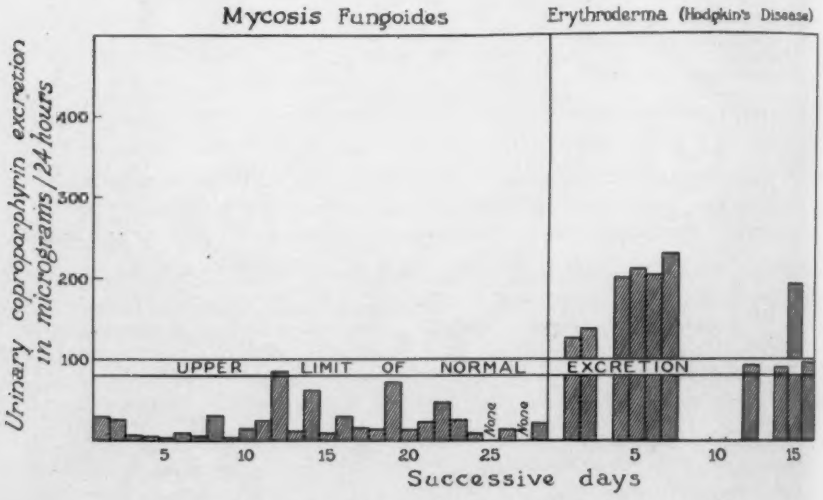

Chart 1.—Porphyrinuria in lymphoblastoma.

other hand, in several cases of generalized erythroderma (3 cases of Hodgkin's disease and 2 cases of leukaemia cutis) there was an appreciable elevation of the amount of porphyrin excreted. In 1 case there was slight intermittent fever; in all cases there was enlargement of the lymph nodes. In this group there was no gross evidence of disturbance of hepatic function. The diagnosis was corroborated in each instance by biopsy of the skin or the lymph nodes or by detailed study of the blood.

Pellagra, Lupus Erythematosus and Sensitivity to Light.—These conditions share the common feature of involvement of the skin of the regions which are most exposed to the natural sun. The relation between sensitivity to light and disturbance of porphyrin metabolism has been a

subject of considerable debate. In our series, in 2 cases of secondary pellagra (not the endemic type) normal excretion of porphyrin was found. In cases of lupus erythematosus of the disseminated type there is frequently sensitivity to sunlight and to ultraviolet or even roentgen rays. In 2 such cases we found normal values for porphyrin in contrast with the report of Ludy and Corson.[15] In 1 case of discoid lupus erythematosus there was a temporary increase in the excretion of porphyrin in association with a reaction of intolerance in the form of urticaria after intravenous injections of gold salts. In cases of eczema solare or urticaria solaris the values for porphyrins were normal with 2 exceptions, in which cases there was a slight temporary increased excretion. In cases of dermatitis medicamentosa caused by sulfanilamide there was frequently associated urticaria solaris of the exposed surfaces. With 2 minor exceptions, however, there was no increased excretion of porphyrin.

Syphilis and Tuberculosis.—In cases of systemic disease there is often a profound effect on porphyrin metabolism. However, in 9 cases of latent syphilis and in 2 cases of syphilis in the secondary stage we did not find any abnormality. Syphilis has been said to produce increased excretion of porphyrins, especially while treatment is being given with the arsphenamines.[20e] In cases of extensive exfoliative reaction following the use of neoarsphenamine we noted such changes from normal. In an attempt to ascertain whether hypersensitivity to the arsphenamines could be detected in the early stages by the porphyrin test, we examined 2 patients who had an urticarial exanthem as a reaction to treatment for syphilis (the 2 patients with secondary syphilis aforementioned). In neither case was there an abnormal value for porphyrin. Concerning tuberculous ulcerations of the skin, we observed 1 case of erythema induratum and 2 cases of scrofuloderma and found increased porphyrins to a considerable degree, and this was independent of fever. Otherwise, evidence of systemic tuberculosis was not present in these cases.

Exfoliative Dermatitis Following Administration of Neoarsphenamine.—In 3 cases of syphilis and in 1 case of nonsyphilitic uveitis, neoarsphenamine had been given intravenously in moderate dosage, and reactions of intolerance appeared on the skin. These reactions proceeded to universal exfoliative dermatitis in each instance. Studies were made of the amounts of porphyrin excreted in the urine and the feces in each instance. Uniformly these values were high; in 2 cases there was six or seven times the normal porphyrinuria during twenty-four hours (chart 2). As the symptoms subsided over a period of weeks, these values slowly returned to normal. The peak of excretion in 2 cases

occurred between the fifteenth and the twentieth day of the reaction, but in both cases there was slight evidence of abnormality by the end of the first week. In 2 other cases, in which there was a slight urticarial reaction to arsphenamine received as treatment for syphilis, values for porphyrins were normal; however, the lesions in these cases did not progress and involve the skin universally, nor did they cause a systemic upset incident to the generalized reaction. A simple test to determine early the likelihood of untoward complications from arsphenamine would be desirable. Unfortunately, it is indicated by our experience that the

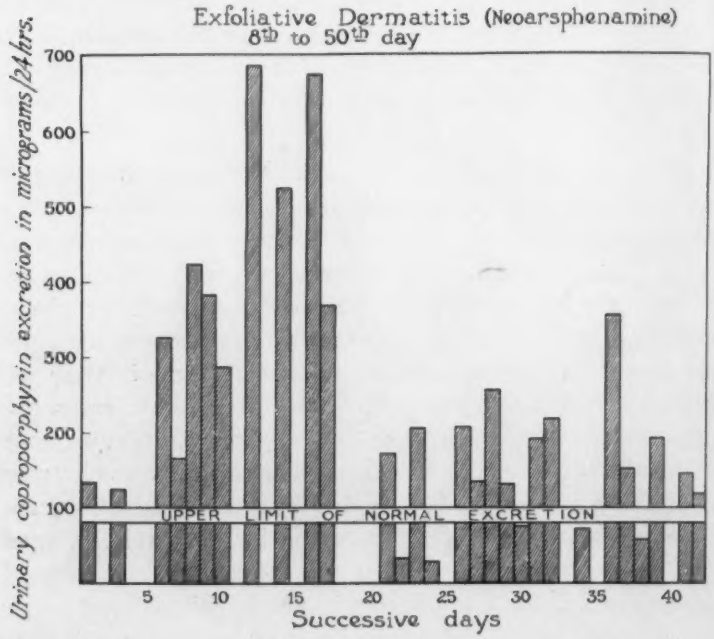

Chart 2.—Porphyrinuria in a case of exfoliative dermatitis caused by neoarsphenamine.

porphyrin metabolism in these cases is not sufficiently upset in the early stages of reaction from arsphenamine to make the test of practical value in such a respect.

Dermatomyositis.—This rare disorder was encountered in 3 persons, and, because of the intimate association of disease of the skin and muscles in these cases with symptoms of systemic disturbance, estimations of porphyrin were made on samples of urine and feces. All specimens were normal, with 1 exception. In a case of a similar wasting

disease of the muscles, myasthenia gravis, there was likewise no evidence of disturbance of porphyrin metabolism.

Ulcerations and Infections.—In cases of multiple abscesses of the skin (staphylococcic) there is an increased excretion of porphyrin, which is enhanced when the febrile reaction is pronounced. If there is extensive destruction of the skin, as in old gasoline burns, an added burden is thrown on the organs of elimination and on the liver; this is likewise reflected in increased excretion of porphyrins (chart 3). In cases of pyoderma gangraenosum in which there are multiple embolic streptococcic abscesses with ulceration of the skin in association with

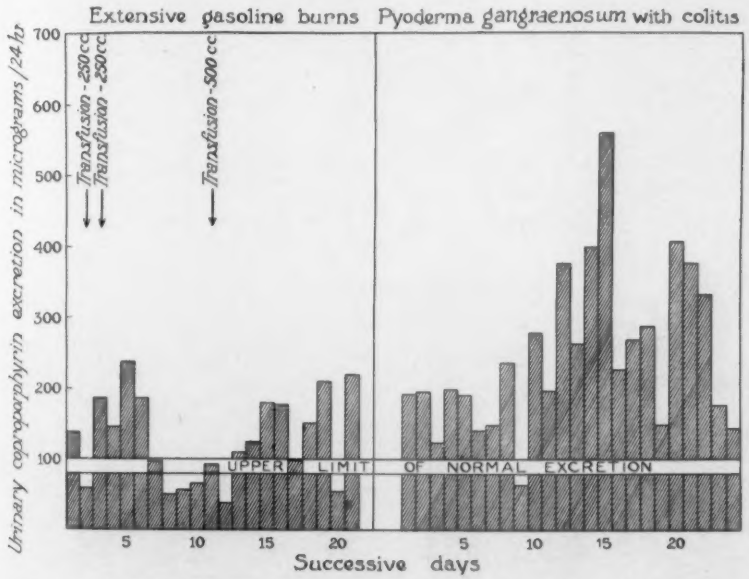

Chart 3.—Porphyrinuria in cases of extensive ulceration of the skin.

episodes of ulcerative colitis, there is a severe disturbance systemically; in such a case we observed consistently a high degree of porphyrinuria; at times the concentration of porphyrin in the urine approached that encountered in the cases of exfoliative dermatitis caused by severe reactions to the arsphenamines.

Effects of Treatment and Miscellaneous Factors.—With fever there is usually increased porphyrinuria, although the relation is irregular and not proportional. Fever induced by the injection of foreign protein, such as typhoid vaccine or boiled whole milk, produces a temporary rise in the amount of excreted porphyrins. The same is true after the administration of whole blood intravenously or intramuscularly (chart 4). The intramuscular injection of whole blood in doses of from 10 to 15 cc.

has often been used as an empiric treatment of psoriasis and for the relief of pruritus in eczema and kindred disorders. In some cases we noted mildly increased porphyrinuria after several such treatments had been given. The same phenomenon was observed after the intramuscular administration of autogenous serum after the solid elements of blood had been removed. Under such conditions and only after such measures of treatment were there any abnormal values for porphyrins in cases of psoriasis and of eczema.

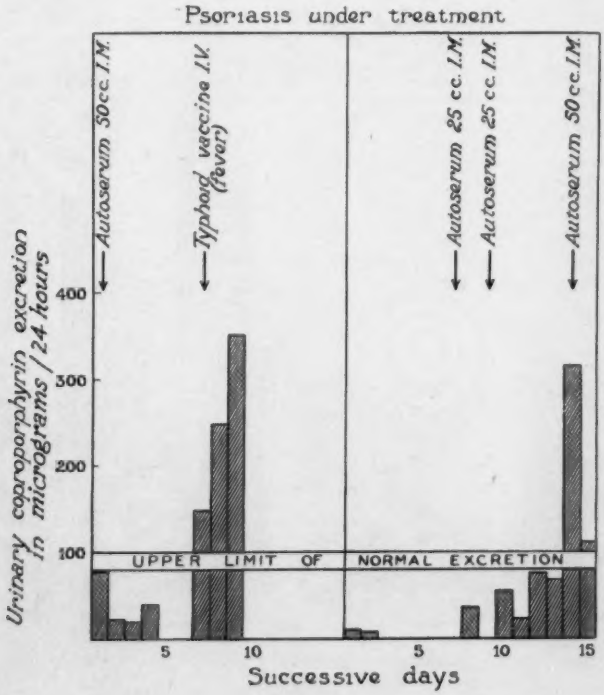

Chart 4.—Porphyrinuria in psoriasis under exceptional circumstances.

SUMMARY

Quantitative estimations of the amount of excreted porphyrins associated with various dermatologic conditions indicate that appreciable increases occur in the elimination of ether-soluble porphyrins (coproporphyrin) in association with disorders accompanied with severe derangement of the general metabolism. Uroporphyrin was not demonstrated. When fever was present or when it was induced artificially, the values for porphyrin in the urine were usually elevated, although not always and not in proportion to the severity of the febrile reaction.

The most significant increase in porphyrinuria occurred in cases of exfoliative dermatitis, after a reaction of sensitivity to neoarsphenamine.

Less striking but nevertheless definite porphyrinuria was noted (1) in cases of extensive ulceration of the skin, both of streptococcic and of tuberculous origin; (2) in cases in which the skin had been denuded by extensive burns after explosion of gasoline; (3) in several cases of generalized erythroderma in association with Hodgkin's disease and leukaemia cutis but not with mycosis fungoides, and (4) in cases of erythema multiforme bullosum and of pemphigus vulgaris but not in a case of pemphigus foliaceus.

Cases of hydroa vacciniforme or congenital porphyria were not encountered. The ordinary sensitivity to light does not affect the excretion of porphyrin; nor does pellagra or lupus erythematosus of the discoid or disseminate type. Likewise, in cases of latent syphilis and in cases of the common dermatoses, such as psoriasis and eczema, the excretion of porphyrins is not affected, except in certain unexplained instances attending the intramuscular injection of whole blood or autoserum.

Excretion of porphyrins in the feces was abnormally high in only 1 case of pityriasis rosea in which the urinary excretion of porphyrin was within normal limits and in 4 instances of exfoliative dermatitis caused by neoarsphenamine.

Further investigation is being made of excretion of porphyrins in cases of syphilis early in the course of treatment, in order to apprehend reactions of sensitivity to the arsphenamines in the incipient stage.

NEUROSYPHILIS IN THE NEGRO

SAMUEL GOLDBLATT, M.D.

WITH THE COLLABORATION OF ELEANOR VANDOREN

CINCINNATI

Reports of routine studies of the spinal fluid of unselected Negroes with syphilis are lacking in the literature. Data on routine repeated periodic examination of the spinal fluid of either Negroes or white persons are extremely scanty. The difficulties of obtaining this type of material are many and various. However, of 5,585 cases of syphilis in Negroes treated in the dermatovenereologic division of the Shoemaker clinic since 1928, an examination of the spinal fluid was obtained as a routine before treatment was started in 1,643 (29 per cent). In an additional 5 per cent the first examination of the spinal fluid was obtained after treatment had been started. Of a total of 1,871 cases in which this diagnostic puncture had been made, a routine examination of the spinal fluid was given after each course of treatment in 718 (38 per cent). A course of treatment consisted of ten injections of a trivalent arsenical or twenty injections of a mercury or bismuth preparation.

Twenty-eight per cent of specimens of spinal fluid were obtained by lumbar puncture, while 72 per cent were obtained by the cisternal route. It was found that the reaction was almost four times as frequent after lumbar (9.7 per cent) as after cisternal puncture (2.5 per cent).

For statistical analysis of the findings on the spinal fluid it becomes necessary, as was pointed out by Moore and others, to make use of some arbitrary type of classification. The general classification of the spinal fluid according to the degree of abnormality indicated by four criteria is given in the tabulation following:

Group	Wassermann Reaction	Globulin Reaction	Cells per Cu. Mm.	Colloidal Benzoin or Gold Curve
1	Negative	Positive or negative	10-20	000 000 333 000 000 0 0 0 3 3 3 3 3 0 0 0
2	Weakly positive	Positive	20-100	000 000 333 000 000 0 0 0 3 3 3 3 0 0 0 0 021 221 333 310 000 0 1 2 5 5 5 3 0 0 0
3	Strongly positive	Positive	30-100 10-30* 10-30†	333 333 321 000 000 5 5 5 5 5 4 3 2 1 0

* Large lymphocytes.
† Polymorphonuclear cells.

Aided by a grant from the Works Progress Administration.

Read before the Section on Dermatology and Syphilology at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 16, 1938.

Dr. Thomas Parran, Surgeon General, and Dr. Raymond Vonderlehr, Assistant Surgeon General, United States Public Health Service, collaborated with Eleanor Vandoren.

Group 1 (mild) comprises spinal fluid in which the lymphocyte count is 10 or more, with or without a positive globulin test; the Wassermann test and the colloidal benzoin or gold curve are normal.

Group 2 (moderate) comprises spinal fluid in which the cell count and the globulin content are increased; the Wassermann test is positive or weakly positive, and the colloidal benzoin or gold curve is indeterminate or positive—usually in the syphilitic zone when positive.

Group 3 (severe) comprises spinal fluid showing the so-called formula of dementia paralytica: marked excess of globulin, a strongly positive Wassermann reaction (in 0.2 cc. or less) and a colloidal gold or benzoin curve of the type of dementia paralytica. The cell count is above normal, and there are, in addition to small lymphocytes, large lymphocytes and polymorphonuclear leukocytes.

This classification is a modification of the one originally suggested by Moore,[1] and its value has been demonstrated both by Moore and by the Cooperative Clinical Group in previous papers. The suitability of this classification in recording the response of spinal fluid to treatment was fully borne out in my material.

TABLE 1.—*Stage of Syphilis*

Diagnosis	Males (919)	Females (724)
Primary	8.27%	1.52%
Secondary	13.38%	14.50%
Latent	42.44%	58.70%
Late active	33.51%	22.10%
Congenital	2.39%	3.18%

INCIDENCE IN PRELIMINARY TESTS OF SPINAL FLUID

The stages of syphilis in which examinations of the spinal fluid were made are shown in table 1. The finding of primary syphilis in the male six times as frequently as in the female well illustrates the hidden character of the initial infection in the female. In secondary and congenital syphilis the distribution between male and female patients was about equal. It is apparent that syphilis runs a milder course in the female than in the male. The incidence of latent syphilis is significantly higher in female than in male patients. Conversely, a higher proportion of male patients had late active syphilis.

Deviations from normal in the spinal fluid were found in all types of clinical syphilis. Thus, patients with primary and secondary syphilis showed 14 per cent, patients with latent syphilis 12 per cent and those

1. Moore, J. E.: Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933, p. 467.

with congenital syphilis 16 per cent of clinically unsuspected abnormalities. In the late active phases of this disease 33 per cent showed pathologic changes in the spinal fluid.

The distribution of the most common types of organic involvement is shown in chart 1. The percentages of cardiovascular, of late cutaneous and of osseous syphilis were smaller than those reported in the literature, since they were calculated from the total number of cases investigated, and not from just those of late active disease, as is the usual practice. In neural and cardiovascular syphilis again the preponderance of male over female subjects was apparent.

The widespread idea that Negroes suffer little from involvement of the central nervous system is erroneous. However, in only 12 per cent of cases of involvement of the central nervous system was this of the

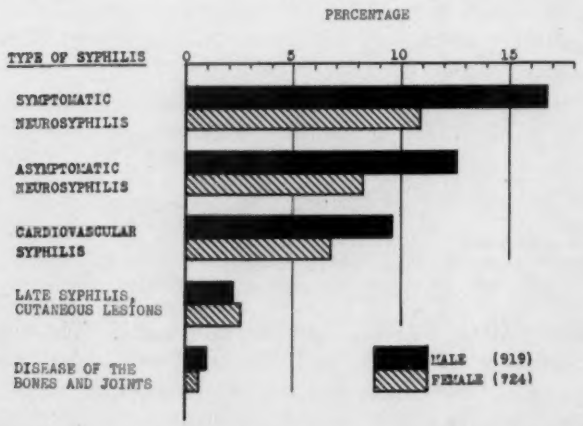

Chart 1.—Classification according to type of involvement of 1,643 patients given preliminary examination of the spinal fluid.

more advanced and severe types (tabes 3 per cent, dementia paralytica 4 per cent, atrophy of the optic nerve 5 per cent). While Negroes have definitely milder forms of neurosyphilis than white persons and Negresses a smaller incidence and milder forms of neurosyphilis than Negro men, it must not be overlooked that 25 per cent of Negroes examined as a routine suffered from some form of neurosyphilis.

Seventy per cent of patients with vascular neurosyphilis had normal spinal fluid, while among those suffering from tabes, the largest number (50 per cent) had group 2 fluid. Sixty per cent of patients with dementia paralytica showed a definite formula of dementia paralytica. A large percentage (66 per cent) of patients whose condition was diagnosed as meningovascular syphilis had normal spinal fluid, but, as this group included all patients with miscellaneous signs of involvement of the central nervous system, the figure is not surprising.

The influence of age on the production of both asymptomatic and symptomatic neurosyphilis is shown by an age curve for the total patients as well as one for those with asymptomatic and those with symptomatic neurosyphilis (chart 2). The curve for asymptomatic neurosyphilis parallels—in fact is almost superimposed on—the curve for total patients, and the mean age for the total patients and that for the asymptomatic group was 32 years. This probably means that asymptomatic neurosyphilis is found, among Negroes at least, in approximately the same proportion in all age groups. The curve for the symptomatic group begins from six to eight years later and reaches its mean at 38 years of age. Thus, in 410 cases in which a definite history of the disease was obtained, 48 per cent of asymptomatic neurosyphilis was found within

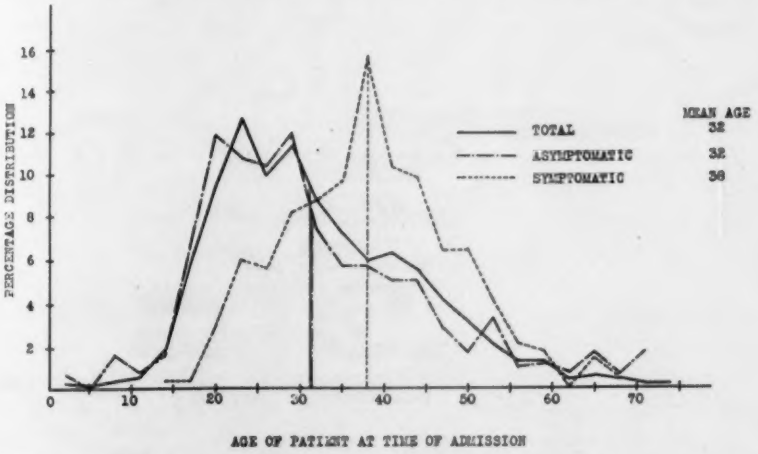

Chart 2.—Age distribution of total number of patients (1,643), of those with asymptomatic neurosyphilis (176) and of those with symptomatic neurosyphilis (234) in the group receiving preliminary examination of the spinal fluid.

one to five years after the contraction of the disease, while symptomatic neurosyphilis occurred between eight and fifteen years after contraction of the disease—that is, about eight years later than asymptomatic neurosyphilis. These findings are in general accord with the observations of the Cooperative Clinical Group.[2]

When the incidence of asymptomatic and of symptomatic neurosyphilis is considered graphically by the degree of abnormality of the spinal fluid in relation to age and sex (chart 3), the fact that asymptomatic neurosyphilis tends to occur at an early age while symptomatic neurosyphilis increases with advancing age is demonstrated again. In asymptomatic neurosyphilis, as the age increases the type of abnormality

2. O'Leary, P. A., and others: Ven. Dis. Inform. **18**:45 (March) 1937.

of the spinal fluid tends to become more severe. This, however, is not true in symptomatic neurosyphilis.

A comparison of the results of the Cooperative Clinical Group as far as Negroes are concerned with my material indicates that the percentage of females with asymptomatic neurosyphilis was the same in both groups, while in my group there were 3.5 per cent more males with asymptomatic neurosyphilis. So far as symptomatic neurosyphilis is concerned, the percentages for females were again in agreement, while the percentage of males in my group (16.9 per cent) was only half, or a little more than half of that reported by the Cooperative Clinical Group (30.7 per cent). The latter difference was due, in all probability, to the fact that my patients were unselected, while the Cooperative Clinical Group

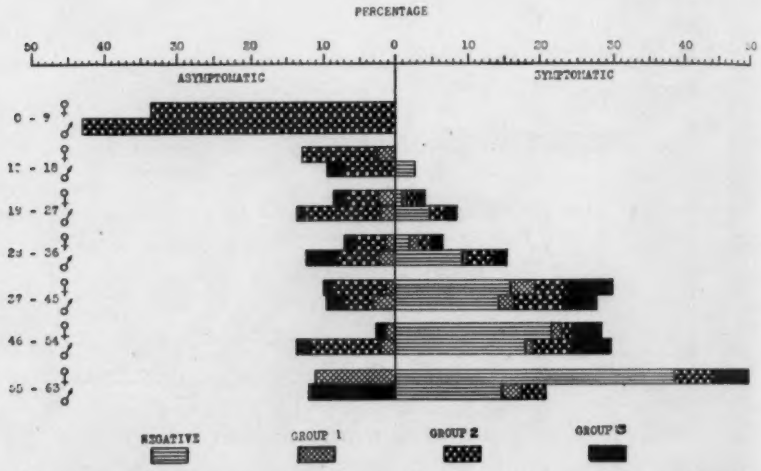

Chart 3.—Incidence and degree of change in spinal fluid in neurosyphilis according to age and to sex.

studied the spinal fluid usually when there were indications of cerebrospinal involvement.

Symptomatic neurosyphilis in Negresses with early syphilis in our group was negligible as compared to an incidence of 6 per cent in the material of the Cooperative Clinical Group. Only 1 per cent of our male patients with early syphilis showed symptomatic neurosyphilis, as compared to 11 per cent in the studies of the Cooperative Clinical Group. Asymptomatic neurosyphilis in Negresses with early syphilis was half again as frequent in patients studied by the Cooperative Clinical Group (11 per cent) as in my group (7 per cent). Ninety per cent of my male subjects with early syphilis showed normal spinal fluid, as compared to 78 per cent reported by the Cooperative Clinical Group.

In late syphilis, however, the relations were changed. The frequency of asymptomatic neurosyphilis among Negresses in my group (9.3 per

cent) was 2 per cent above that in the group studied by the Cooperative Clinical Group (7.5 per cent). Symptomatic neurosyphilis among females was half again as frequent in my group (18 per cent) as in the material of the Cooperative Clinical Group. The males of my group showed an increased incidence of 6 per cent over the males studied by the Cooperative Clinical Group, so far as asymptomatic neurosyphilis was concerned, but only about half as much symptomatic neurosyphilis (25 per cent) as those studied by the Cooperative Clinical Group (42 per cent).

INCIDENCE IN CASES IN WHICH THERE HAD BEEN NO TREATMENT OR IN WHICH TREATMENT HAD LAPSED

When the spinal fluid is periodically examined after the preliminary examination, certain unsuspected phenomena are demonstrable. In a group of 71 cases of varying stages of syphilis in which a number of examinations of the spinal fluid were given but no treatment was instituted the condition of the spinal fluid in 25 per cent fluctuated. The reactions became positive in twice as many (16 per cent) as they became spontaneously negative (9 per cent). In 75 per cent of cases in which there had been no treatment the spinal fluid, examined at intervals varying from six months to four years, remained unchanged.

In a group of 32 cases in which examination of the spinal fluid had been made before and after lapses from therapy varying from six months to six years, the reactions in 3 per cent became positive. An average of nine injections, three of an arsenical and six of a heavy metal, even though irregularly administered, was apparently sufficient to prevent a shift of the reaction of the spinal fluid from negative to positive.

INCIDENCE IN CASES IN WHICH THERE HAD BEEN TREATMENT

Six hundred and eighty-seven patients with syphilis of all types had preliminary examination of the spinal fluid and repeated examinations following courses of treatment. Of these, 410 patients had neurosyphilis, of whom 43 per cent had asymptomatic and 57 per cent symptomatic neurosyphilis. Many patients did not continue treatment beyond one or two courses. In fact, at the beginning of each new course of treatment approximately one half of the patients under treatment in the previous course had dropped off. This explains the different figures used to arrive at various facts—only those patients who received all of the courses to a specified result are utilized.

When the reactions of the spinal fluid reversed to negative the reaction of the blood reversed in 38 per cent of cases, as compared with only 10.5 per cent when the reactions of the spinal fluid remained

positive. Although in 38 per cent of the cases reaction of the blood failed to reverse to negative when those of the spinal fluid did, in more than twice as many (79 per cent) the reaction of the blood remained positive when the spinal fluid was fast. The difference in percentage is large enough to be significant.

The efficacy of treatment in changing positive reactions of blood and spinal fluid to negative is shown in chart 4, in which are listed all examinations of the spinal fluid in cases in which a blood test had been made within ten days and the amount of previous treatment was known. All treatment was included, even though given the patient prior to admission to the Shoemaker clinic. This chart demonstrates that of the patients who had no treatment 5.8 per cent had negative reactions of

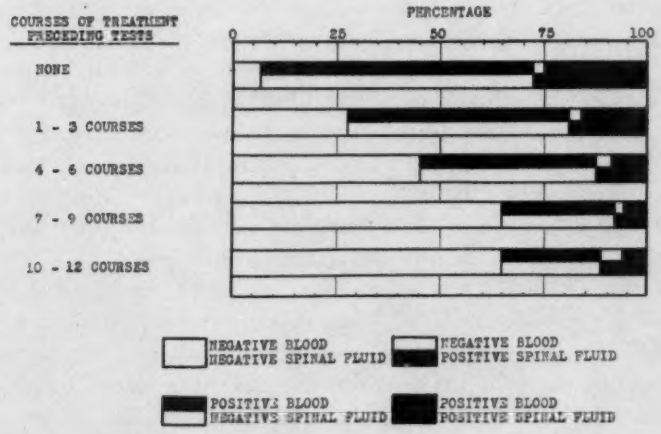

Chart 4.—Reactions of blood and spinal fluid of syphilitic Negroes in relation to amount of treatment.

both blood and spinal fluid. This percentage steadily increased as courses of treatment were given, so that of tests made after thirteen to fifteen courses of treatment 75 per cent gave negative results. The percentage of cases in which both the blood and the spinal fluid gave positive reactions decreased from 25 per cent in cases in which no treatment had been given to 6 per cent after ten or twelve courses of treatment.

When no treatment had been given, the percentages of positive reactions of the spinal fluid which accompanied positive and negative reactions of the blood were not significantly different.

The blood test is a valuable guide to the status of the spinal fluid. In fact, its significance increases with the adequacy of therapy. Wassermann fastness of the blood after seven to nine courses of therapy is likely to be accompanied with abnormality of the spinal fluid four times as frequently as is a negative reaction of blood produced by treatment.

In cases in which there had been no treatment the percentage of positive reactions of the blood was the same in association with negative and with positive reactions of the spinal fluid. In cases of normal spinal fluid the incidence of the positive reaction of the blood decreased steadily, from 92 per cent before treatment to 30 per cent after seven to nine courses. When the reaction of the spinal fluid was positive the decrease in percentage of positive reactions of the blood was much less striking—from 90 per cent before treatment to 67 per cent after seven to nine courses. In other words, when the reaction of the spinal fluid has remained positive after seven to nine courses of treatment, the possibility of a positive reaction of the blood is more than twice as great as when the spinal fluid is normal.

The stronger the positive reaction of the spinal fluid, the less likely was the blood to be normal. The percentage of negative reactions of the

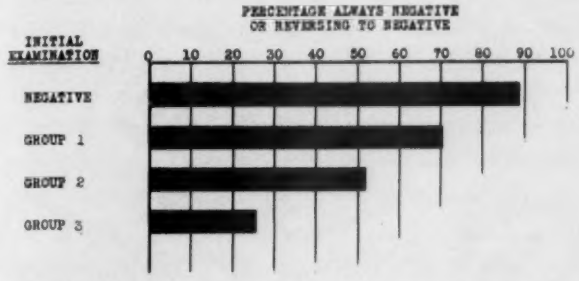

Chart 5.—Classification of reversals of reactions of spinal fluid to negative according to type of abnormality.

blood decreased from 34 per cent when the spinal fluid was normal to 9 per cent when the spinal fluid showed the more abnormal type of curve characteristic of dementia paralytica.

Fluctuations occurred in the spinal fluid in 128 cases in which four or more examinations of the spinal fluid were made. All cases in which the specified number of tests had been given were included, regardless of whether the examinations were made after consecutive courses of treatment. This does not significantly violate the premise on which this study is based, for in the 128 cases in which four examinations had been made four courses of treatment was the average. A similar situation existed with regard to the 71 cases in which five or more examinations were made. In these an average of five courses of treatment was given.

When the reaction of the spinal fluid (88 per cent) was negative on the first examination (chart 5), it usually stayed negative throughout the course of treatment for syphilis. Spinal fluid of group 1 responded favorably to therapy in 70 per cent of cases. Favorable response of

group fluid 2 occurred in 50 per cent, while in only 25 per cent of cases in which the formula of dementia paralytica was present was there a favorable reaction to administration of chemotherapeutic drugs.

SUMMARY AND CONCLUSIONS

The feasibility of routine pretherapeutic and repeated examination of the spinal fluid was demonstrated in 1,871 cases.

Reactions to lumbar puncture were four times as frequent as reactions to cisternal puncture. No serious or fatal reactions were noted with either technic.

Routine pretherapeutic examination of the spinal fluid gave the following results:

1. The female had less frequent and milder neural and cardiovascular syphilis than the male.

2. A greater incidence of asymptomatic neurosyphilis than previously reported was discovered, showing that the percentage of neurosyphilis in the Negro tends more nearly to approximate that in the white race.

3. Organic involvement of the central nervous system was demonstrated earlier.

4. Eighty per cent of neurosyphilis in Negroes was of the mild type.

5. The incidence of asymptomatic neurosyphilis according to age was shown to parallel that of syphilis; symptomatic neurosyphilis tended to make its greatest appearance about eight years later.

6. Unsuspected abnormality was found in the spinal fluid in an average of 14 per cent of all cases of syphilis, exclusive of those of late active disease in which abnormality fo the spinal fluid occurred in 33 per cent.

7. In cases of vascular and meningovascular neurosyphilis the spinal fluid tended to be normal.

8. The more positive the reaction of the spinal fluid, the less likely was the reaction of the blood to be negative.

9. The great bulk of asymptomatic neurosyphilis occurred during the first five years after contraction of the disease, while most symptomatic neurosyphilis occurred during the eight to fifteen year period following contraction of the disease.

Repeated examination of the spinal fluid in cases of untreated syphilis indicated that the reaction progresses to positive twice as often as it spontaneously regresses.

In cases of therapeutic lapse an average of nine injections of chemotherapeutic drugs was apparently sufficient to prevent spontaneous progression in the spinal fluid.

Repeated examination of the spinal fluid after courses of treatment indicated:

1. The blood test is a valuable guide to the status of the spinal fluid. Its significance increases with the adequacy of therapy.

2. When the spinal fluid changes to normal the reaction of the blood is likely to reverse. This occurred in 38 per cent of cases. When the reaction of the spinal fluid remained positive, that of the blood remained positive after therapy in 79 per cent of cases.

3. Adequate therapy in patients with positive reactions of blood and spinal fluid usually causes reversal to negative. This occurred in 75 per cent of cases.

4. A positive reaction of the blood after the completion of adequate therapy will be accompanied with abnormal spinal fluid four times as often as will a negative reaction of the blood at that stage.

5. If the reaction of the spinal fluid has remained positive after adequate therapy, the possibility of a positive reaction of the blood is more than twice as great as when the spinal fluid has become normal.

Spinal fluid which was normal at the beginning of treatment rarely showed fluctuations throughout the course of therapy. A favorable response to treatment was obtained in 70 per cent of cases in group 1, 50 per cent in group 2 and 25 per cent in group 3.

259 Doctors Building, Garfield Place.

ABSTRACT OF DISCUSSION

DR. MARQUE O. NELSON, Tulsa, Okla.: There is still a widespread belief that Negoes do not have syphilis of the nervous system. If there could have been any doubt of their having it, Dr. Goldblatt's work furnishes ample evidence that they do, and that routine testing of the spinal fluid shows abnormality in a percentage of cases comparable with that in white persons. Of course, this is not the same as saying that late symptomatic neurosyphilis, especially of parenchymatous type, is as common in the Negro; in fact, Dr. Goldblatt's figures confirm accumulated experience already on record, that late symptomatic neurosyphilis easily recognizable by the clinician is definitely less common in Negroes than in white persons.

A reason often suggested to explain this is the supposed immunity to the disease acquired by the Negro from extensive lesions in the skin. This may explain part of it, but probably not all. I would rather believe that other factors are more important: hereditary differences in the nature and construction of the vascular system and of the tissues of the central nervous system and natural physiologic and immunologic differences in the entire body.

In his conclusions Dr. Goldblatt says that nine injections of a therapeutic drug are apparently sufficient to arrest spontaneous progression of the disease into the spinal fluid. One should not conclude from this that symptomatic progression in all cases of syphilis of the central nervous system can be checked by that amount of treatment. A good deal more than that is usually necessary, and in many cases no amount of treatment with chemotherapeutic drugs is of any value whatever.

The value of examination of the spinal fluid as a guide to treatment is once more brought out, especially in cases with a colloidal curve in the first zone. In such cases ordinary treatment is too often largely a waste of time, and fever therapy should be used without too much preparation or delay.

There is still a practice of examining spinal fluid by the Wassermann test alone. It should not be necessary to mention that at least three tests should be done on the spinal fluid as a guide to treatment: the Wassermann test, the cell count and the determination of the colloidal benzoin curve. I believe that the colloidal benzoin determination is definitely superior and more sensitive than the colloidal gold and more dependable.

Dr. E. L. Merritt, Fall River, Mass.: I should like to ask one question in connection with the blood tests that are done for comparison with the findings in the spinal fluid.

In Massachusetts the State Department of Health for some time has been using the Hinton test, and it has been rather illuminating to find, over a period of several years, the number of cases in which there were positive Hinton tests while the Wassermann test was repeatedly negative. I should like to ask Dr. Goldblatt what type of blood test he refers to when he speaks in his paper of blood tests. I think it is rather important to determine whether the test is a Kahn, a Wassermann or a Hinton test, because in a rather large series of cases the Wassermann test showed absolute serologic negativity regarding the blood, whereas a definitely positive reaction was obtained on repeated Hinton tests.

Dr. A. A. Herold, Shreveport, La.: In Louisiana, where a large proportion of the population is Negro, there is a dictum that the black Negro never has neurosyphilis. I should like to ask Dr. Goldblatt if he has made any distinction between the pure Negro and the Negro with mixed blood in his study of neurosyphilis. I have observed in the clinic that this impression is erroneous and that invariably black Negroes who have been untreated or insufficiently treated for syphilis give a 4 plus Wassermann reaction of the spinal fluid and frequently an abnormal colloidal benzoin curve.

Dr. Samuel Goldblatt, Cincinnati: I want to thank Dr. Nelson particularly for bringing out a point which might have been misconstrued. The average of nine injections which I described as preventing spontaneous progression in the spinal fluid does not hold for the prevention of the development of somatic neurosyphilis. As a matter of fact, I frequently observed the development and progression of somatic neurosyphilis in association with a negative reaction of the spinal fluid in cases in which partial treatment had been given. The Wassermann, the Kahn and the Kline test were given, both the diagnostic and the exclusion Kline being used simultaneously in all cases. I have had no experience with the Hinton test. As far as Dr. Herold's question is concerned, I am unable to tell by the color of the skin whether a Negro is pure blooded or not. Black Negroes frequently have mothers or fathers with mixed blood. Our studies revealed no difference in the development of somatic neurosyphilis or change in the spinal fluid which could be correlated with the color of the skin of the patient.

CIRCUMCISION IN TREATMENT OF CHANCROIDAL LESIONS OF MALE GENITALIA

FURTHER OBSERVATIONS

JOHN E. RAUSCHKOLB, M.D.
CLEVELAND

In 1929 a group of 537 cases of lesions diagnosed as chancroidal infections of the male genitalia was reported from the dermatologic service of the Cleveland City Hospital.[1] These cases were all those of penile chancroidal infection observed for a period of four and a half years (July 1924 to January 1929).

In an effort to decrease the length of stay in the hospital and to reduce the incidence of complicating suppurative inguinal adenitis, which occurred in at least 50 per cent of the patients before or during hospitalization, an attempt was directed toward increasing peripheral drainage and exposing inaccessible lesions by circumcision.

Ricord[2] in 1858 abrogated circumcision in the management of chancroidal infection. Aubert[3] in 1882 lent his support to the contrary view, claiming that healing by first intention frequently occurred in patients with chancroids who were circumcised. Salsotto[4] in 1892 circumcised 5 such patients; in only 1 case was healing delayed by autoinfection. Carle[5] contributed 14 cases in which patients with chancroid were circumcised in 1904. In the United States, Bellenger[6] in 1902 reported the first circumcision for chancroid. In 1918 Van Winkle[7]

Read by title at the Sixty-First Annual Meeting of the American Dermatological Association, Inc., Del Monte, Calif., June 9, 1938.

From the Department of Dermatology and Syphilology of the Western Reserve University School of Medicine, and from the Cleveland City Hospital, service of Drs. H. N. Cole and J. R. Driver.

1. Rauschkolb, J. E.: Circumcision: Its Value in the Treatment for Chancroidal Lesions of the Male Genitalia, Arch. Dermat. & Syph. **21**:251 (Feb.) 1930.
2. Ricord, P., cited by Carle: Le traitement chirurgical du chancre mou, Semaine méd. **24**:273, 1904.
3. Aubert, P.: De la réunion immédiate dans l'opération du phimosis compliquant le chancre simple, Lyon méd. **34**:301, 1882.
4. Salsotto, G.: Sulla opportunità di operare il fimosi che complicá l'ulcera venerea, Morgagni **34**:247, 1892.
5. Carle: Le traitement chirurgical du chancre mou, Semaine méd. **24**:273, 1904.
6. Bellenger, B. L.: Circumcision for Chancroids and Other Causes, New Orleans M. & S. J. **55**:347, 1902.
7. Van Winkle, J. S.: Circumcision in the Presence of Chancroids, U. S. Nav. M. Bull. **12**:712, 1918.

recorded 28 cases in which the method was used. Newman [8] in 1920 treated 9 patients by circumcision, without lymphatic complications. In 1927, Stuempke [9] pointed out as indications for circumcision lesions on the internal surface of the prepuce, lesions otherwise inaccessible to local treatment and lesions so situated that circumcision might largely remove the infected area by excision. He stipulated that the operation should be conducted with the region under local anesthesia, and complete postoperative rest in bed for a few days was advised to prevent development of buboes.

One hundred and seventy-one cases of circumcision for chancroid were added to the literature by 1929. Conclusions were drawn from this group which definitely established the value of circumcision in the treatment of chancroid: (1) the accessibility of the ulcers after circumcision has made the care of the lesions much easier; (2) buboes have developed in no patient treated by circumcision; (3) in many instances an early diagnosis of syphilis has been possible from what was formerly an inaccessible primary infection, and (4) the actual time the patients spent in the hospital after circumcision has compared favorably with the number of days spent by patients treated nonsurgically.

PURPOSE OF THIS PAPER

In the intervening years, from 1929 to 1938, no further contribution with reference to circumcision in cases of chancroidal infection has been found in the literature. It is the purpose of this paper to add 247 additional cases of chancroidal infection treated by circumcision. In the nine year period from 1929 to 1938 there have occurred 479 cases of penile lesions diagnosed as chancroidal infection in the dermatologic service of the Cleveland City Hospital. This small number of cases may be explained on the basis of a more accurate diagnosis obtained through the recovery of Haemophilus Ducrey from the lesion and the routine use of the intradermal reaction by means of sterilized chancroidal pus or vaccine.

Of the patients in this group, 322 were Negroes and 157 were white, a ratio of 2 to 1. When the ratio of Negroes to white persons in the urban population of Cleveland (1 to 12) is considered, the high incidence of this disease in the Negroes is significant.

The patients varied in age from 15 to 72 years, with a mean age of 28.01 years. The average age of the Negro patients was 26.85 years and that of the white patients 30.42 years.

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8. Newman, S.: Complete Circumcision in Chancroid Beneath Tight Prepuce and Multiple Chancroids on Prepuce, Virginia M. Monthly **47**:311, 1920.

9. Stuempke, G., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 21, p. 122.

SOURCE OF INFECTION

Promiscuous coitus among the socially unenlightened and economically unfortunate was the invariable history of the source of the infection. In 5 patients infection with Haemophilus Ducrey developed in penile lesions of scabies which antedated the chancroidal infection.

DURATION OF DISEASE AT TIME OF HOSPITALIZATION

In Cleveland, patients with penile lesions are admitted to the municipal hospital whenever possible to insure thorough diagnostic study and efficient treatment. There is also a public health aspect. Patients with such lesions who apply to the outpatient clinics throughout the city are usually hospitalized shortly after their initial contact with the clinic. Frequently they have had more or less treatment, both local and constitutional, and apply for admission only as the disease continues to progress. The shortest stated duration of the disease before hospitalization was one day; the longest, one and one-half years; the average for the entire group, 39.32 days. For the 322 Negro patients the average duration of ulceration before hospitalization was 44.90 days, as compared with an average of 28.72 days for the 157 white patients. In such a lengthy period of extramural duration of infection ample opportunity is afforded for growth in size and number of the lesions, increased liability to complications, such as buboes, balanitis and phlebitis of the dorsal vein, and more activity in disseminating similar infections.

CHARACTER OF THE LESIONS

In this series, the shorter the duration of infection before the patient entered the hospital, the more likely was the ulceration to be small and single. With the protracted average duration of five to six weeks, the vast majority of the patients, particularly the Negroes, had multiple lesions. The most common sites of the lesions were, in the order named, the preputial orifice, the internal surface of the prepuce, the frenum, the glans penis and the fossa navicularis.

In 11 patients, 8 of whom were Negroes, spread of the process from the penis to other localities was recorded. In 3 instances additional lesions were noted on the perineum; in 2 instances, on the anus; in 2, on the scrotum; in 2, on the thigh; in 1, on the abdomen, and in 1, on the right thumb.

Of the entire series of 479 cases, the chancroidal infection in 231, or 48.22 per cent, was complicated by buboes. One hundred and sixty-one of these occurred in Negroes and 70 in white patients. The Negro patients reported an average duration of the complicating adenitis of 17.23 days before admission; the white patient, an average duration of 14.61 days. Thirty-three Negro patients had bilateral buboes on admission, as compared with 5 white patients who had similar complications.

Seven of these 33 Negro patients had draining bilateral buboes when they entered the hospital. Among the unilateral buboes 15 in the Negro patients were draining at the time of admission to the hospital, as compared with 11 in the white patients.

The location of the primary process was generally reflected in the location of the complicating inguinal buboes and in the determination of unilateral or bilateral inguinal adenitis. The longer the duration of the infection, the greater was the incidence of inguinal adenitis. Interference with peripheral drainage by phimosis or escharotic agents contributed directly to the development of buboes.

METHOD OF DIAGNOSIS

The diagnosis of chancroidal infection was determined by one or more of the following methods:

1. Recovery of Haemophilus Ducrey from the lesion.
2. Determination of the intradermal reaction for chancroid with (*a*) bubo pus or (*b*) specific vaccine.
3. Autoinoculation by the technic of Ravaut.
4. Evaluation of clinical signs and symptoms.

Thick smears, preferably taken from exudate at the undermined border of the lesion, were fixed and stained with Giemsa's or Wright's stain and were examined microscopically under an oil immersion lens. Of the 479 cases in which the lesions were considered chancroids, reports of examination for Haemophilus Ducrey in the smear were available in 297 instances. The specific organism was identified in 167 cases, or 56 per cent, of the group so examined. Diagnosis of chancroid in these cases was positive.

With the technic of Cole and Levin,[10] 0.1 cc. of diluted, sterilized chancroidal bubo pus was injected intracutaneously on the flexor surface of the forearm. Establishment of a diagnosis was sought in 190 of the total series of 479 cases by means of this test with chancroidal antigen. In a few cases similarly tests were made with a bacillus of Haemophilus Ducrey (Dmelcos vaccine). One hundred and sixty patients showed a positive reaction, as determined by the appearance of an infiltrated, rounded papule at least 0.5 cm. in diameter forty-eight hours after the injection. A positive reaction was interpreted as showing that the patient now had or at some previous time had had a chancroidal infection. A negative result was interpreted as meaning that the lesion was too recent to produce a positive reaction or was not chancroidal. The usual time required for the host to build up a positive reaction was five weeks. Objective symptoms of the penile lesion were

10. Cole, H. N., and Levin, E. A.: The Intradermal Reaction for Chancroids with Chancroidal Bubo Pus, J. A. M. A. **105**:2040 (Dec. 21) 1935.

necessary to sustain a diagnosis of chancroidal infection even when the reaction to the antigen test was positive.

Resort to autoinoculation as a method of diagnosis was considered necessary in only a few puzzling cases. In 12 cases in which Haemophilus Ducrey was not recovered from the penile lesion an attempt was made to autoinoculate the patient by inoculating a scarified area of his thigh with exudate from the original lesion. In all 12 cases the autotransplant was successful. In 10 of these cases Haemophilus Ducrey was recovered from the area of autoinoculation. No patient so treated was able to leave the hospital in 32.47 days, the average stay for the entire series. Hospitalization was increased 10 per cent at the very least and in 11 of the 12 cases was lengthened 25 to 75 per cent. Search for Haemophilus Ducrey and intradermal tests for chancroids have gained preference in diagnostic study. Nevertheless, in certain moot cases the Ravaut technic of autoinoculation is a justifiable procedure. It should never be done, however, outside a well regulated hospital ward.

There have always been cases in which the specific organisms cannot be found in stained smears, in which no positive intradermal reaction to chancroidal antigen can be obtained, in which search for Spirochaeta pallida and Donovan bodies yields persistently negative results, in which no positive Frei reaction can be obtained and in which all clinical signs nevertheless point toward the diagnosis of chancroid. One hundred and forty cases in this series have been included as satisfying these requirements.

RELATION OF CHANCROID TO SOME OTHER VENEREAL INFECTIONS

When chancroidal infection occurred with other venereal disease the clinical signs of infection with Haemophilus Ducrey tended to overshadow other types of infection.

Syphilis.—One hundred and fifty-four diagnoses of syphilis were made in conjunction with diagnoses of chancroidal infection in the total series of 479 cases. One hundred and fifteen patients with complicating syphilis were Negroes; 39 were white. The syphilis was in the primary stage in 61 cases, was secondary in 36 cases and was latent or tertiary in 57 cases.

The incidence of complicating syphilis in this series of chancroidal infections was 32 per cent. The incidence of primary syphilis was 12.7 per cent, and that of active secondary syphilis was 7.5 per cent.

Lymphogranuloma Venereum.—No Frei antigen tests were performed in this series prior to 1931. Subtraction of the cases in this series occurring before 1931 leaves a group of 320. One hundred and ninety-four Frei antigen tests were done in this group. There were 36 positive reactions, 34 among the Negro patients and 2 among the

white. In these cases the penile lesions were recognized as typical chancroidal lesions by recovery of Haemophilus Ducrey or were clinically diagnosed by interpretation of a positive intradermal reaction to chancroid antigen. Differential diagnosis in these cases as to the cause of the inguinal adenitis was difficult.

Granuloma Inguinale.—In 2 cases in the entire series, 1 observed in 1929 and 1 in 1933, the patients in both being Negroes, concurrent diagnoses of granuloma inguinale and chancroidal infection were made by identification of Donovan bodies and Haemophilus Ducrey.

TREATMENT

Local Therapy.—Pending establishment of a diagnosis, patients with penile lesions uncomplicated by suppurative buboes were ambulatory. All patients with suppurative inguinal adenitis were confined to bed during this period of observation for diagnostic work-up.

In the course of the nine year period extensive experience was had with a great variety of local agents. Detergents, such as soap and

TABLE 1.—*Syphilis as a Complication of One Hundred and Fifty-Four of Four Hundred and Seventy-Nine Cases of Chancroid*

	Primary Syphilis	Secondary Syphilis	Latent Syphilis
White	19	10	10
Negro	42	26	47
Total	61	36	57

water, artificial gastric juice and soaks and compresses of boric acid, potassium permanganate in a dilution of 1 : 8,000 up to 1 : 10,000, hydrogen peroxide and diluted solution of sodium hypochloride U. S. P. were widely used. Topical applications of solution of formaldehyde, phenol and alcohol, Mencière's solution,[10] gentian violet, Rosenwald's formulas[11]

10. Mencière's solution consists of iodoform, 10 Gm.; guaiacol, 10 Gm.; eucalyptol, 10 Gm.; 95 per cent alcohol, 10 Gm.; peruvian balsam, 30 Gm., and ether, 100 Gm.

11. Rosenwald's formulas:

A.	Parts by Volume
Mild mercurous chloride	30
Zinc sulfate	60
Camphorated tincture of opium	60
Solution of calcium hydroxide U. S. P.	240

Shake well, apply on cotton to lesion

B.	Parts by Weight
Zinc oxide	30
Starch	30
Boric acid	30
Camphor	30
3% phenolated petrolatum	360

A and B and cod liver oil ointment were tried at various times. Powders, such as iodoform, were used. Heat was employed as moist heat in the form of hot compresses and soaks and as dry heat afforded by a carbon filament bulb attached to a cradle over the bed. A radium plaque and roentgen irradiation to the local lesions were tried in a limited number of cases.

Gradually a routine local therapy became established, consisting of treatment with detergents and hot soaks or compresses of saline solution until a diagnosis of chancroid was made. Soaks of saline solution were then replaced with hot potassium permanganate (1 to 8 parts in 10,000) applied four times a day, aided by alternate drying of the lesions, dusting with iodoform powder and application of dry heat furnished by the lighted cradle over the bed.

Foreign Protein.—Foreign proteins, such as typhoid vaccine given intravenously or milk and whole blood given intramuscularly, were used at various times. Occasionally a patient with chancroid complicating syphilis of the central nervous system was given malaria therapy. Intravenous injection of typhoid vaccine was the most extensively used foreign protein therapy. It was used in 157 cases and seemed to give the patient whatever benefit leukocytosis and hyperpyrexia could afford him in overcoming the chancroidal infection.

Systematic Treatment.—Intravenous injections of antimony and potassium tartrate in a limited number of cases produced no improvement in the chancroids. Intravenous injections of arsphenamine and mapharsen given to patients who had syphilitic lesions on the genitalia seemed to produce improvement by healing the syphilitic lesions and removing a locus minoris resistentiae for chancroidal infection.

Vaccine and Bubo Pus Antigen.—A specific vaccine of Haemophilus Ducrey (Dmelcos vaccine) was used in 7 cases intramuscularly three times a week in graduated doses from 0.1 to 1 cc., with varying results. In each instance the vaccine was used as an adjunct to the routine therapy. The average period of hospitalization for patients so treated was 28.57 days as compared with an average period of 32.47 days for the entire group.

Eight patients were treated with bubo antigen pus in similar manner. In 1 case the treatment gave a striking clinical result. The average period of hospitalization for this small group was 16.1 days.

Circumcision.—Indications: Circumcision was recommended whenever indicated as prophylaxis against bubo, to relieve phimosis and paraphimosis and to render inaccessible lesions visible for critical diagnostic study and efficient treatment. Technic: Two hundred and forty-seven patients of the 479 submitted to circumcision (which was done by interns under the supervision of resident physicians). The technic

was as follows: The patient was prepared for operation with a hypodermic injection of ¼ grain (0.016 Gm.) of morphine sulfate and $\frac{1}{150}$ grain (0.004 Gm.) of scopolamine hydrochloride. Anesthesia was secured by block with 2 per cent solution of procaine hydrochloride without epinephrine, injected through one dorsal and one ventral needle puncture, a 2 inch, 21 gage needle being used. With the penis anesthetized, the field was thoroughly scrubbed with a hand brush and soap and water. After strong traction the prepuce was amputated by the guillotine method. Free bleeding was encouraged. The free edge was scrubbed, and complete hemostasis was secured. Coaptation of the skin and mucous membrane was secured by a collar of ten to twelve ordinary skin clips buckled with a transversely placed clip at the frenum. The patient's thighs were strapped together with 2 inch (5 cm.) adhesive tape. A suspensory bandage was applied. The wound was dusted with iodoform powder, and the patient was returned to bed without a dressing and kept there for three to five days under a cradle continuously heated with a carbon filament bulb. Hot, freshly prepared potassium permanganate soaks in 1:8,000 up to 1:10,000 dilution were employed for ten minutes four times a day. All débris was thoroughly removed with gauze by the patient after each soaking. After this débridement, the wound was dried and dusted with iodoform powder. A physician performed this cleansing thoroughly with soap, water and hydrogen peroxide each morning. The clips were left in place until the incision healed, whether this took seven or fourteen days. They were gradually removed, those at the dorsal and ventral midpoints being left until the last.

Autoinoculation along the line of incision was almost invariably encountered but was never troublesome when this postoperative routine was used. The area around the frenum and any portion of the line of incision that traversed the ulcerations were generally the last places to heal.

A simple dorsal slit was never employed. Occasionally patients entered who had been subjected to this procedure three to fourteen days before admission to relieve paraphimosis or phimosis. Usually the spread of infection in these cases suggested phagedena and increased and complicated hospitalization. It was felt that the difference in result between the method used for them and that practiced by us was due in part to different preparation and operative technic but especially to different postoperative care. Circumcision for chancroidal infections is a hospital procedure.

EFFECT OF CIRCUMCISION ON BUBOES

In 16 cases, 13 of the patients being Negroes, the inguinal adenitis spontaneously regressed after circumcision. In these cases no further

treatment of buboes was necessary. Six patients, 3 Negroes and 3 white persons, not treated by circumcision likewise showed spontaneous subsidence of the inguinal adenitis. No bubo, however, that had become fluctuant ever receded spontaneously, regardless of the type of therapy used in managing the penile lesions.

Among the 247 patients circumcised no bubo was found after operation if it had not existed preoperatively.

HOSPITALIZATION

The entire series of 479 patients was readily divided into 247 patients circumcised and 232 not circumcised. The average period of hospitalization for the circumcised patients was 34.66 days. In this group the average preoperative stay in the hospital was 6.37 days, and the average postoperative sojourn was 28.29 days. This compares favorably with the average period of hospitalization for the noncircumcised patients, 30.13 days. The mean hospital stay for the entire series was 32.47 days.

TABLE 2.—*Period of Hospitalization*

	Circumcised Series (247 Patients)		Noncircumcised Series (232 Patients)	
	White	Negro	White	Negro
Number	67	180	90	142
Average hospitalization after circumcision	31.01 days	27.28 days		
Average hospitalization			23.46 days	34.36 days
Average hospitalization for all after circumcision	28.29 days			
Average hospitalization for all			30.13 days	

One hundred and thirty patients who had no complicating buboes were circumcised, the average postoperative stay in the hospital being 29.83 days. One hundred and seventeen patients with complicating buboes were circumcised, the average postoperative stay in the hospital being 24.23 days. It might seem that the complicating inguinal adenitis really fortified the host by contributing a specific or foreign protein endogenous therapy.

Further analysis of the period of hospitalization seemed interesting when the racial factors were evaluated. There were 322 Negro patients. Of these, 180 were circumcised, and the average postoperative period of hospitalization was 27.28 days, as compared with 34.36 days for the 142 noncircumcised patients. Of the 157 white patients, 67 were circumcised and the average postoperative stay in the hospital was 31.01 days, as opposed to 23.46 days for the 90 patients not circumcised. It would seem that circumcision is more valuable as an adjunct in the treatment of chancroids in Negroes than in white patients.

Experience has suggested that a long, tight prepuce, readily inducing phimosis or paraphimosis on inflammation, is more common in the Negro.

SUMMARY

An additional series of 479 cases of chancroidal infection with 247 instances of circumcision is reported. The study offers further evidence that circumcision can be satisfactorily accomplished in the presence of chancroidal infection under hospital conditions. It may be a valuable adjunct in diagnosis and treatment.

With the technic described, buboes, if not already present, did not develop after circumcision.

One in 8 patients in the series had concurrent primary syphilis.

The average stay in the hospital for the entire series of 479 patients was 32.47 days.

The average postoperative stay in the hospital in 247 cases in which circumcision was done was 28.29 days.

Postoperative treatment is described.

UVEOPAROTITIS

A SARCOID REACTION

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Uveoparotitis is an unusual clinical syndrome which because of the renewed interest of dermatologists in diseases of the glandular system has become extremely interesting. The precise nature of the condition is not known, but because of the association of uveitis with tuberculosis and because a tuberculoid structure is seen in the microscopic sections of glands in uveoparotitis, tuberculosis has been suspected as the cause even though definite experimental proof is lacking. When complete, the syndrome consists of bilateral enlargement of the parotid glands and uveitis. As a consequence of the inflammation, such common symptoms as fever, neuritis with palsy, toxic eruptions and involvement of the adjacent glands are frequently recorded.

The question of nomenclature must be considered here, for in our opinion this syndrome is a part of generalized sarcoid and therefore might be labeled lymphogranuloma benignum, Hutchinson-Besnier-Boeck disease or sarcoidosis.[1] In order to emphasize the enlargement of the parotid glands, we have entitled our dissertation "Uveoparotitis."

HISTORY AND LITERATURE

As far as can be ascertained, the first case of typical uveoparotitis was recorded in 1899 by Daireaux [2] and Pechin,[3] who described a characteristic example occurring in a man 22 years of age. There

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From the Division of Dermatology, University of Minnesota, Henry E. Michelson, Director.

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1. Hunter, F. T.: Hutchinson-Boeck's Disaese (Generalized Sarcoidosis), New England J. Med. **214**:346, 1936.

2. Daireaux, P.: Paralysis faciale et iritis d'origine ourlienne; des neurites ourliennes, Bull. méd., Paris **13**:227, 1899.

3. Pechin, A.: Complications oculaires des oreillons (iritis et keratite), Rec. d'opht. **2**:336, 1901.

was bilateral parotid swelling with iritis, and later paralysis of the facial nerve developed. The observers considered the disease an atypical form of mumps.

The first case in the United States was recorded in 1904 by Cutler,[4] but it was not until 1909 that that author [4a] reported a classic example. He expressed the belief that the condition was Mikulicz' syndrome accompanied with iritis, because of the simultaneous involvement of the parotid and the lacrimal glands, and that some hematogenously carried agent inducing lymphoid hyperplasia was the cause.

The literature has since been much enriched, with the articles of de Paoli [5]; Heerfordt,[6] who proposed the name uveoparotitis; Lehman,[7] who saw the syndrome in 3 tuberculous patients; Carmody,[8] who recorded 15 examples of tuberculosis of the parotid; MacBride[9]; Levin,[10] who stressed the neurologic findings; Berg,[11] who produced a splendid review; Rogers and Bodman [12]; Hamburger and Schaffer,[13] who reported a case of Mikulicz' syndrome involving the parotid glands; Cavara,[14] in whose case tuberculosis was definitely proved to be the cause; Souter,[15] who reported the autopsy of a patient who had had uveoparotitis for six months prior to death; Cunningham [16]; Merrill

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4. Cutler, C. W.: Symmetrical Enlargement of Parotid and Lachrymal Glands; Nodular Iritis, Tr. Am. Ophth. Soc. **10**:390, 1904.

4a. Cutler, C. W.: Lesions of the Cornea in Gonorrheal Ophthalmia and Phlyctenular Keratitis, Am. J. Obst. **59**:706, 1909.

5. de Paoli, E.: Tuberculosi della parotide, Atti e rendic. d. Accad. med.-chir. di Perugia **5**:172, 1893.

6. Heerfordt, C. F.: Ueber eine Febris parotidea subchronica an der Glandula parotis und der Uvea des Auges lokaliziert und häufig mit Paresen cerebrospinaler Nerven kompliziert, Arch. f. Ophth. **70**:254, 1909.

7. Lehman, K.: Om febris uveo-parotidea, Hospitalstid. **9**:117, 1916.

8. Carmody, T. E.: Tuberculosis of the Parotid Gland, Laryngoscope **24**: 873, 1914.

9. MacBride, H. J.: Uveoparotitic Paralysis, J. Neurol. & Psychopath. **16**: 242, 1823.

10. Levin, P. M.: The Neurological Aspects of Oveoparotid Fever, J. Nerv. & Ment. Dis. **81**:176, 1935.

11. Berg, F.: Om "febris uveo-parotidea" (Heerfordt), Hygiea **85**:401, 1923.

12. Rogers, B., and Bodman, J. H.: Case of Parotitis with Iritis, Bristol Med.-Chir. J. **43**:84, 1926.

13. Hamburger, L. P., and Schaffer, A. J.: Uveoparotid Fever as Manifestation of Mikulicz's Syndrome, Am. J. Dis. Child. **36**:434 (Sept.) 1928.

14. Cavara, H.: Pathology of a Subchronic Case of Uveoparotitis, Bull. d'ocul. **7**:925, 1928.

15. Souter, W. C.: A Case of Uveo-Parotid Fever with Autopsy Findings, Tr. Ophth. Soc. U. Kingdom **49**:113, 1929.

16. Cunningham, H. M.: Tuberculous Parotitis: Report of a Case, Laryngoscope **40**:116, 1931.

and Oaks,[17] who collected 30 cases and reported them in 1931; Mohn,[18] who reported an example of the disease associated with erythema nodosum; Garland and Thompson,[19] who gave the title "uveoparotid tuberculosis" to the syndrome; Tanner and McCurry[20]; Savin[21]; Cohen and Rabinowitz[22]; Folger[23]; Gram and Illingsworth,[24] whose patient had a pulmonary picture consistent with sarcoid, and Coogan,[25] whose patient also had cervical tuberculosis.

Up to the present more than 70 cases have been reported in the literature, and the reader is referred to the recent article of Waldenström,[26] of Uppsala, Sweden, for an exceptionally fine discussion of the entire situation.

SYMPTOMS OF UVEOPAROTITIS

Uveoparotitis today consists of inflammation of the parotid glands and iritis, with usually a third and variable complication. The onset of the disease is not constant and may be ushered in with the symptoms of grip. Neither is the length of time between prodromal symptoms and the appearance of the syndrome fixed. In some patients several months was necessary before well established uveoparotitis was recognized.

(1) *Parotid Glands.*—In typical uveoparotitis both glands become enlarged simultaneously. Although one gland may be affected first, as a rule enlargement of the other soon follows. The swelling begins in the preauricular area, with marked uneven nodular induration, but in spite of the inflammation there is little discomfort or pain, even on palpation. The inflammation apparently is well confined within

17. Merrill, H. G., and Oaks, L. W.: Uveoparotitis with Case Report, Am. J. Ophth. **14**:15, 1931.

18. Mohn, A.: Ein Fall von Febris uveo-parotidea (Heerfordt), Acta ophth. **11**:397, 1933.

19. Garland, H. G., and Thompson, J. G.: Uveo-Parotid Tuberculosis, Quart. J. Med. **2**:157, 1933.

20. Tanner, S. E., and McCurry, A. L.: Uveoparotid Tuberculosis, Brit. M. J. **2**:1041, 1934.

21. Savin, L. H.: An Analysis of Signs and Symptoms of Sixty-Six Published Cases of Uveo-Parotid Syndrome, with Details of an Additional Case, Tr. Ophth. Soc. U. Kingdom **54**:549, 1934.

22. Cohen, S. J., and Rabinowitz, M. A.: Uveoparotitis, J. A. M. A. **105**:496 (Aug. 17) 1935.

23. Folger, H. P.: Uveoparotitis (Heerfordt): Report of a Case, Arch. Ophth. **15**:1098 (June) 1936.

24. Gram, F., and Illingsworth, R. S.: Uveoparotid Tuberculosis, Lancet **2**:245, 1936.

25. Coogan, D. G.: Uveoparotid Fever, Am. J. Ophth. **18**:637, 1935.

26. Waldenström, J.: Ueber gutartige, universelle, tuberkuloide Granulome mit besonderer Berücksichtigung der Uveoparotitis, Zentralbl. f. d. ges. Tuberk.-Forsch. **15**:249, 1936.

the capsule of the gland, and the periglandular tissues are free; thus, the overlying skin is not adherent to the mass. Mastication is not interfered with, except by dryness of the mouth.

Besides the parotid glands, the other salivary glands are often simultaneously or subsequently involved, and even though the parotid swelling remains about the same size, the submaxillary glands may swell and subside several times during the course of the disease. The cervical supraclavicular nodes and even the hilar lymph nodes are occasionally affected. Involvement of the latter may often be demonstrated in roentgenograms of the chest, an important finding etiologically. Cutler [4] observed generalized adenopathy in his patient.

The swelling of the parotid glands usually lasts from two to six months, although in Merrill and Oaks's [17] case the glands remained enlarged for three years. The lymph nodes recede with the process, and enlarged hilar glands are not found after the condition has become quiescent. The parotid swelling, then, is a gradual, hard, uneven induration, practically painless, lasting for several months and receding without suppuration. It apparently is a localized response to an agent which may affect other glandular structures. Complete resolution is the rule. Dryness of the mouth (xerostoma) is a frequent result of the parotid inflammation.

(2) *Ocular Symptoms.*—Ocular symptoms are practically always bilateral. The patient may complain of burning of the eyes, slight photophobia and misting or blurred vision. Iridocyclitis is the most common ophthalmic symptom and occurs in its characteristic form. The course and sequelae of the ocular symptoms are not unusual, but relapse may occur without renewal of the parotid inflammation. It is important to remember that there is nothing about the ocular symptoms in this syndrome which makes possible a diagnosis of uveoparotitis on that basis alone.

(3) *Complications.*—Paralysis of the facial nerve is the most common neurologic complication because of the intimate association of the facial nerve with the parotid gland. It is noted in about 50 per cent of reported cases. Bilateral palsy also has been seen, and a more or less generalized peripheral neuritis of varying degrees of severity is not uncommon. Levin [10] reviewed the neurologic aspects of the syndrome and gave a good summary of the possibilities.

Cutaneous eruptions constitute one of the less common features of the syndrome. They occur in less than one third of the reported cases. Also in several instances integumentary changes preceded the other diagnostic criteria by several months.

A blotchy erythema of the lower extremities resembling erythema nodosum is the most frequent eruption recorded, but urticarial and

macular types of toxic erythema have been seen. The cutaneous lesions of this syndrome are not pathognomonic and point to a toxic cause. Garland and Thompson [19] observed a case of papulonecrotic tuberculid associated with uveoparotitis.

Fever accompanying the disease was stressed by Heerfordt [6] when in 1909 he named the syndrome, but later investigators have not put much emphasis on this symptom.

HISTOLOGIC PICTURE OF THE PAROTID GLAND IN CASES OF UVEOPAROTITIS

The histologic picture of the parotid glands in all accumulated reports of biopsy has been strikingly similar; in fact, it is the most uniform part of the syndrome. Sections were taken from the parotid glands in the cases reported by Reimers,[27] Müller,[28] Weve,[29] Cavara,[14] Souter,[15] Dorrell,[30] Garland and Thompson [19] and Tanner and McCurry,[20] and in our 2 cases. In all of these the diagnosis was hyperplastic or epithelioid tuberculosis without caseation. Tanner and McCurry were able to demonstrate tubercle bacilli, even though the patient's reaction to tuberculin was negative. We were unable to demonstrate tubercle bacilli in our sections. Histologic investigation of the hilar nodes was reported only in Souter's case. The glands in that case had been entirely replaced by a tuberculoid infiltrate.

In our first case a biopsy specimen was taken from the lower pole of the right parotid gland and was diagnosed by the hospital pathologist as tuberculous. Our examination of the section showed that about half of the parotid tissue was replaced by a tuberculoid structure consisting of closely packed epithelioid cells and an occasional giant cell. There were practically no lymphocytes. Here and there were areas of homogeneous matter resembling liquefaction but unlike caseation necrosis. We interpreted these areas to be pressure changes in certain parotid acini. In most of the tubercles no necrosis was seen.

The microscopic sections in our 2 cases were similar and would permit a diagnosis of sarcoid because of the closely packed epithelioid cells, the occasional giant cells and the lack of lymphocytes and necrosis.

ETIOLOGY

No definite etiologic agent has been proved for uveoparotitis. Heerfordt [6] favored some infectious agent probably closely related to that

27. Reimers, O.: Ueber einen Fall von Febris uveoparotidea und ueber die Beziehungen zur Tuberkulose, Ztschr. f. Augenh. **60**:30, 1926.

28. Müller, M.: Bemerkungen zu der Arbeit von H. Rieth über Iridozyklitis bei Parotitis epidemica und anderen Speicheldrüsenschwellungen und über ihre Beziehungen zur Tuberkulose, Klin. Monatsbl. f. Augenh. **64**:387, 1920.

29. Weve, H.: Familiäre, Uveo-parotides unbekannten Ursprungs, Klin. Monatsbl. f. Augenh. **78**:83, 1927.

30. Dorrell, E. A., cited by Garland, H. G., and Thompson, J. G.: Uveo-Parotid Tuberculosis (Febris Uveo-Parotidea of Heerfordt), Quart. J. Med. **2**:157, 1933.

of mumps, but this explanation seems unlikely because of the lack of epimediologic association, the long course and the microscopic picture.

The ocular manifestations of the syndrome are of the type that ophthalmologists diagnose as tuberculous, without, however, finding the bacilli. The assumption of a tuberculous cause is reasonable but has not been proved. Buchs [31] studied a number of cases and concluded that the condition was a special form of tuberculosis of the iris. In all cases in which histologic sections have been made from specimens of the iris, they have been interpreted as tuberculoid infiltration. The tuberculin test in 21 cases was done and gave a negative result in all but 4. If we favor an alinement of the condition with sarcoid, this is in keeping with our knowledge of that condition. The negative reactions to tuberculin may be looked on as evidence of positive anergy because of the general well-being of the patient and the benign course of the parotitis.

Seefelder [32] had the opportunity to study clinically and examine histologically lesions of the eye of a patient with sarcoid of the skin and bones. The lesions were entirely consistent with the pathologic changes elsewhere in the body.

The type of keratic precipitates which occur in nearly one half of the cases in which the iris is involved may be indicative of tuberculosis, syphilis or leprosy. The last disease can be ruled out easily by a thorough clinical study; thus far in no cases have evidences of leprosy been found. In no case in which the Wassermann and the precipitation tests for syphilis were positive has there been any therapeutic response to antisyphilitic therapy. It is definitely believed, therefore, that in these instances syphilis was coincidental. Tuberculosis again appears to be the most likely cause of the keratic precipitates in uveoparotitis.

Some observers have linked uveoparotitis with Mikulicz' syndrome, which consists of painless enlargement of the salivary and lacrimal glands. According to Thursfield,[33] Mikulicz' syndrome may be congenital or hereditary or may occur in association with many chronic diseases, such as leukemia, tuberculosis and lymphosarcoma. The histologic picture of uveoparotitis differs markedly from that of Mikulicz' syndrome, except in instances in which tuberculosis is the etiologic agent of the syndrome, in which a differential diagnosis is difficult to make.

Four deaths have occurred in cases of uveoparotitis. In 3 of these, death was due to miliary tuberculosis. In Lehman's case death was due to pernicious anemia associated with pregnancy.

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31. Fuchs, E.: Lehrbuch der Augenheilkunde, ed. 15, Leipzig, Franz Deuticke, 1928, p. 521.

32. Seefelder, R.: Ein weiterer Beitrag zu den Augenveränderungen bei der Besnier-Boeckschen Krankheit, Arch. f. Augenh. **110**:415, 1937.

33. Thursfield, H., cited by Rees, W. E.: Mikulicz Syndrome in Association with Tuberculosis, Lancet **2**:749, 1934.

REPORT OF CASES

CASE 1.—Mrs. C. H. D., a patient of Dr. Lawrence Larson, aged 24, was 5 feet 6½ inches (169 cm.) tall and weighed 125½ pounds (56.9 Kg.). She was examined on March 13, 1936, at which time she stated that she had been in good health until four years previously, when urticaria developed. This was present off and on for one year and was followed by leukoderma of the face and neck. At the time of examination she complained of a burning sensation in the epigastrium, coming on immediately after she ate and lasting from one to one and a half hours. Eight weeks before she had noticed a swelling over both

Fig. 1 (case 1).—Uveoparotitis.

parotid glands, which gradually increased for three weeks but remained stationary for the succeeding five weeks. She had not had fever so far as she knew and had not lost any weight. She had an eccentric pear-shaped right pupil, which her mother stated had been present when she was a baby and which the patient remembered distinctly to have been present eight years before when she entered high school.

She had had smallpox, measles and whooping cough in childhood.

Family History.—Her maternal grandmother died of cancer of the breast at the age of 58. Her maternal grandfather died of an undiagnosed gastric ailment at the age of 60. Her father was killed in an accident at the age of 37. Her

mother was living and well at the age of 52; three sisters were living and well. The patient had spent several days visiting two sisters-in-law who had pulmonary tuberculosis.

Physical Examination.—Eczema of the occipital region of the scalp was revealed. The pupil of the right eye was eccentric in that it was pear shaped and drawn nasally, where it was bound down to the lens by adhesion. There was a mass the size of a small walnut in the region of the isthmus of the thyroid. There was marked swelling in the region of both parotid glands. The blood pressure was 104 systolic and 72 diastolic; the pulse rate was 90, and the temperature was 97.8 F.

Laboratory Tests.—A blood count showed 88 per cent hemoglobin, 4,400,000 red cells and 6,200 white cells. The blood smear revealed many monocytes, some with vacuolated cytoplasm. The smear was examined by Dr. Hal Downey, who reported that the most important feature of the blood was the presence of many monocytoid reticuloendothelial cells; some of these had vacuolated cytoplasm and so appeared histiocytic; the majority of them were intermediate between reticuloendothelial cells and monocytes and did not show histiocytic features.

Mantoux tests with 1:1,000 and 1:500 dilutions gave negative results. Examination of the urine for tubercle bacilli by smear as well as by inoculation of a guinea pig gave negative results. The Kolmer and the Wassermann test of the blood were negative. Agglutination tests for typhoid, paratyphoid and Malta fever gave negative results. The electrocardiogram showed no abnormality.

Roentgen examination of the gastrointestinal tract, with administration of a barium enema, of the bones of the hands and feet, of the long bones and of the pelvis showed no abnormality, with the exception of a small exostosis of the medial side of the upper end of the right tibia and one small cystlike area at the base of the medial spine of the right tibia. Roentgenograms of the chest showed marked swelling of the glands at the hili of the lungs but not at the bifurcation. Disseminated throughout both lungs and more apparent in the lower part than in the upper was a fine discrete mottling.

The gastric analysis gave normal results.

Progress.—The condition remained stationary until May 1936, when the swelling of the parotid glands decreased but swelling of the submaxillary glands appeared. By the latter part of June the swelling of the parotid and the submaxillary glands was less marked, and the blood smear showed no monocytoid cells having the reticuloendothelial characteristics noted in earlier examinations. The course of the disease, as followed by blood smears, showed the monocytes becoming progressively more mature as the patient improved, although numerous toxic polymorphonuclear cells persisted for a long time. The assumption was that the monocytoid cells of the earliest smears were not reticuloendothelial cells but immature monocytes showing some reticuloendothelial characteristics and that they were derived from the reticulum, which was active at that time.

CASE 2.—F. C., a patient of Dr. William T. Peyton, a 44 year old white farmer, had been apparently well except for measles and mumps as a child until two years prior to his admission to the hospital. At that time he noticed swelling in both parotid glands, which increased gradually and reached its maximum size in about four weeks. He had had no previous discomfort and felt well except for excessive dryness of his mouth, which persisted during the first six months of his illness. For the week before presentation he had pain in both eyes, with blurring and diminished vision. He had consulted various physicians and

clinics during the preceding two years and had received some roentgen and ultraviolet irradiation, with no apparent reduction in the size of the parotid glands.

Physical Examination.—The general physical examination showed no abnormality except for redness of the ocular conjunctiva. No examination of the eyes was performed. The parotid glands could be easily outlined by palpation. They were indurated and divided into lobules. The skin was nonadherent to the glands.

Laboratory Examination.—A blood count showed 95 per cent hemoglobin and 6,300 white blood cells, with 65 per cent neutrophils, 4 per cent eosinophils, 20 per cent lymphocytes and 11 per cent monocytes. The urine was normal. Biopsy of the gland was performed.

A letter received from the patient four years after his discharge stated that he felt entirely well, and no swelling of the parotid glands was noticeable.

Fig. 2 (case 2).—Uveoparotitis.

COMMENT

Unilateral or bilateral gradual enlargement of the parotid glands does not offer many diagnostic possibilities. Mixed cell tumor usually can be diagnosed by the long history, the irregular, stony hard nodules and the fact that it is almost always on one side only. Tuberculosis of the parotid glands is rare, and, according to Carmody,[8] is of two distinct types: (1) a chronic fibroid form, which may well be an example of the condition under discussion, and (2) an acute inflammatory variety, which usually undergoes necrosis. This form occurs in patients with demonstrable pulmonary or oral tuberculosis. It is readily understood that all enlargements of the parotid glands that are not acute require microscopic section for accuracy in diagnosis.

The frequency of paralysis of the facial nerve in uveoparotitis may be explained on the basis of pressure, but paralysis has been reported preceding discernible enlargement of the gland; paralysis has also been seen on the opposite side. So there may be causes of palsy of the nerve other than mere pressure on the trunk.

Multiple neuritis in uveoparotitis has been observed, and so a circulating noxa has been assigned a causative role in the condition.

There are many reasons why the entire syndrome of uveoparotitis may be viewed as a particular form of sarcoidosis, especially when one is willing to view this condition as Wahlgren [34] described it: as a generalized disease which does not involve any one system but by predilection invades the skin, lymph nodes and glands, bones and lungs and even brings about changes in the blood. The criteria for the diagnosis of sarcoidosis are the clinical and histologic observations, the results of roentgen examinations and the biologic and experimental reactions.

Clinically, one must look for:

1. Cutaneous lesions of various types.

2. Generalized involvement of the lymph glands. The patient is often entirely unaware of any swellings.

3. Changes in the tonsils, which may be found only if a biopsy is made.

4. Changes in the bony canal which may go into destruction and even fracture. Bony changes may be subsequent to cutaneous changes. This is especially noticeable in the lupus pernio type of sarcoid, as emphasized by Stoll.[35]

5. Pulmonary findings. There are usually no clinical symptoms, but roentgen examination shows a peculiar mottling which roentgenologists have learned to recognize as characteristic of sarcoid infiltration of the lungs.

6. Enlargement of the liver and spleen. This is present often enough to be considered a frequent accompaniment.

7. Monocytosis. This has often been found and seems to have real significance. Microscopic examination of the involved tissue, regardless of its location, reveals a constant and characteristic collection of epithelioid cells, closely packed and sometimes surrounded by a fringe of lymphocytes, with or without an occasional giant cell. This sarcoid type of inflammation does not go on to necrosis and when absorbed leaves little or no trace in soft tissues and only an atrophic

34. Wahlgren, F.: Bemerkungen über die pathologische Anatomie bei gutartigen Lymphogranulomatosis, Zentralbl. f. Haut- u. Geschlechtskr. **58**:299, 1938.

35. Stoll, H. F.: A Case Presenting Pulmonary and Osseous Lesions Presumably Due to Sarcoid, Ann. Int. Med. **10**:1589, 1937.

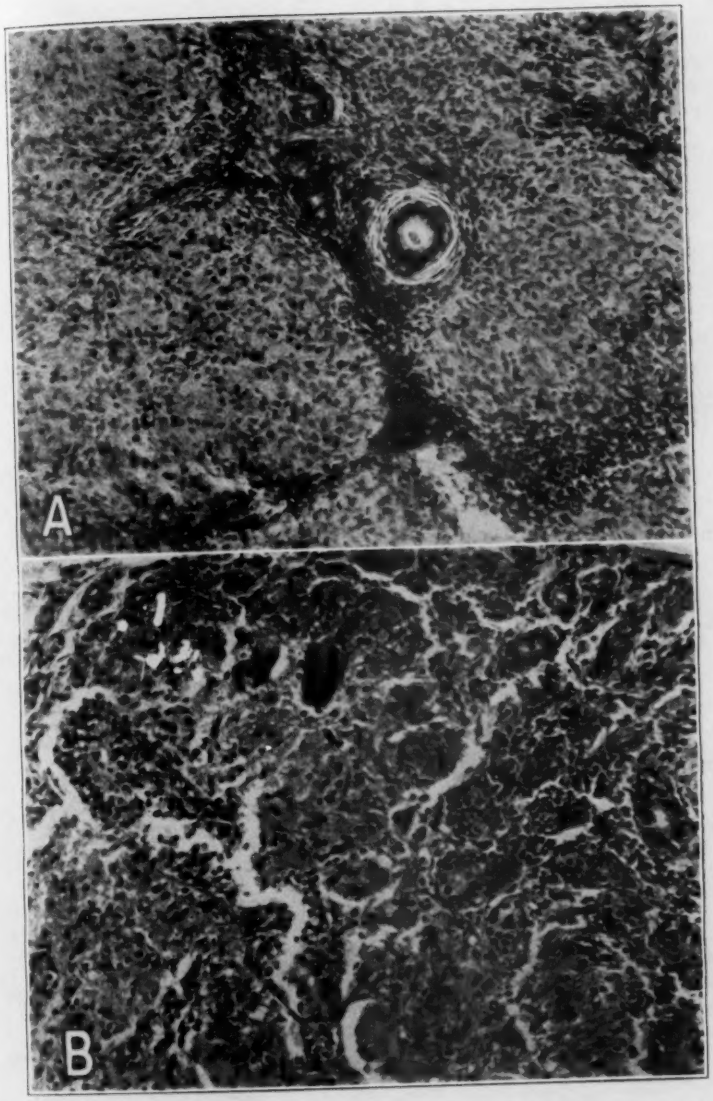

Fig. 3.—*A* (case 1), low power magnification of section from parotid gland, showing reaction; *B* (case 2), section from parotid gland, showing details of sarcoid reaction.

scar in harder tissues. It must be stressed that the histologic structure of the cutaneous lesions is not as certain an indicator as are changes in extracutaneous tissues of certain clinical forms of cutaneous tuberculosis; for example, lupus vulgaris may give an almost perfect picture of sarcoid.

In our experience a biopsy of the tonsil is well worth performing and may give valuable information. Implantation in guinea pigs of bits of the diseased tissue does not produce tuberculosis, and the reaction of the subject to tuberculin is usually negative, upholding the view that the serum contains an antituberculin substance. Because of the general well-being of the patient, the name positive anergy has been given to this state. However, the ultimate prognosis of sarcoidosis must not be too optimistic, for deaths have been and are being more frequently reported. Nickerson [36] had the opportunity to perform autopsy in 6 cases of sarcoid and made several valuable observations and contributions. One startling but not unusual conclusion was that there was no evidence of frank tuberculosis.

Having briefly discussed some of the important facts about sarcoidosis, one is immediately struck by the fact that uveoparotitis and sarcoidosis have many points in common, and that aside from the striking enlargement of the parotid glands in the one, no sharp differentiation is possible. In fact, the similarity or identity of the two is apparent.

Point for point, there are glandular enlargement in both conditions and many reports of enlarged salivary glands in frank sarcoid; involvement of the lacrimal glands often in both conditions; hepatic and splenic enlargement also reported in both; biopsy and autopsy of lymph glands showing indistinguishable pictures in the two diseases, and similar pulmonary lesions and bony changes. Boeck's sarcoid with iritis is by no means rare, and when biopsy is performed the characteristic changes are observed. Fleeting exanthems, fever and various symptoms of acute illness are often reported under one or the other title. In fact, it is next to impossible to distinguish between uveoparotitis and sarcoidosis in certain cases.

A discussion of the cause of sarcoid including uveoparotitis necessarily leads one to accept or reject the proofs of tuberculous origin. Certainly the reason that tuberculosis was first put forth as the cause was the tuberculoid structure invariably found at biopsy. Examples of this structure in other chronic infections, however, are too common to need emphasis. The absence of tubercle bacilli (except in a few cases of early involvement before true sarcoid is formed), the negative

36. Nickerson, D. A.: Boeck's Sarcoid: Report of Six Cases in Which Autopsies Were Made, Arch. Path. **24**:19 (July) 1937.

results of experiments with animals and the negative reaction to tuberculin must be explained before one may willingly accept tuberculosis as the cause of sarcoidosis. The course is not that of tuberculosis, although Mylius and Schürmann [37] have described a form of tuberculosis which is practically indistinguishable from sarcoid. It is hard to conceive of the extensive pulmonary involvement often found, associated with failure to respond to tuberculin and the fact that the sputum remains free from bacilli. The improvement often noted after ingestion of arsenic suggests somewhat a relation to lymphoblastoma. Many reports of sarcoid's changing its character and becoming frank lupus vulgaris are found. Nevertheless, one must realize that the first lesion need not have been a true sarcoid lesion, even though the microscopic section had all the necessary elements for that diagnosis.

The work of the Scandinavian school leads us to believe that lymphogranuloma benignum of Schaumann is a generalized disease and that, regardless of its causes, it cannot be entirely or properly evaluated from a study of the cutaneous lesions alone. Furthermore, there are many cases of sarcoid without any history or trace of lesions of the skin, and if uveoparotitis is accepted as a particular combination of symptoms in sarcoid, it is realized at once that cutaneous lesions are not necessary for the diagnosis, and even if present are a small part of the involvement as a whole.

A virus has been proposed as the cause of sarcoid by Williams and Nickerson,[38] but so far as we know, their work has not been followed as yet with more experiments.

For our own part, we feel that the cause of sarcoid, and hence in our opinion of uveoparotitis, has not as yet been proved, that it is an open question and that in spite of the fact that many authors, by exclusion or conviction, decide that tuberculosis is the likely cause, irrefutable proof is lacking. Darier [39] has aptly said that the lesions of the sarcoid syndrome are not really due to their apparent cause (an infectious agent such as tuberculosis, leprosy or syphilis) but that the real factor is the organism or subject. The infecting agent is only the provoking factor. Sarcoid represents a reaction of the same general type, with varying eventualities provoked in the organism by multiple causes, notably by diverse infections. Their reactional nature makes one comprehend why they do not infallibly respond to treatment.

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37. Mylius, K., and Schürmann, P.: Universelle sklerosierende tuberkulöse grosszellige Hyperplasie, eine besondere Form atypischer Tuberkulose, Beitr. z. Klin. d. Tuberk. **73**:166, 1929.

38. Williams, R. H., and Nickerson, D. A.: Skin Reactions in Sarcoid, Proc. Soc. Exper. Biol. & Med. **33**:403, 1935.

39. Darier, J.: Considérations sur la nature des sarcoïdes, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **41**:999, 1934.

They may respond to or resist various therapeutic procedures. Jordan and Osborne,[40] in an exhaustive and illuminating report, concluded that sarcoid reactions could be provoked by various agents. They expressed the belief that cutaneous sarcoid could be classified morphologically but did not seem willing to include the entire syndrome as a single disease.

Mellon and Beinhauer [41] were able to elicit noncaseating epithelioid lesions in the lungs of guinea pigs with an anomalous variant of the tubercle bacillus. If this variant proves to be the cause of sarcoidosis, then it will be necessary to explain, if possible, what factors bring about changes in the host and the bacilli which make for this form of response and its pathogenesis.

Pautrier [42] found that in his case of Besnier-Boeck disease the differential white blood cell count showed a high percentage of large mononuclear cells. Hematologic examination in our 2 cases likewise showed numerous early monocytes, apparently derived from the reticuloendothelial system. These monocytes varied with the course of the disease; in case 1 they were most numerous and showed the greatest immaturity at the height of the disease and became progressively more mature as the patient recovered. This type of monocyte indicates an increased activity of the reticuloendothelial system.

TREATMENT AND PROGNOSIS

Uveoparotitis, in contrast to other forms of sarcoid, usually undergoes spontaneous resolution, even though recurrence is not uncommon. Therefore, one must not give any particular form of therapy too much credit when cure results. One of our patients received some treatment with roentgen rays and eventually recovered completely, while our second patient was given 0.025 Gm. of sodium gold thiosulfate intravenously at weekly intervals for two months and experienced rather pronounced diminution in the swelling of the parotid glands.

The prognosis for patients with uveoparotitis is good. The condition subsides within a few months, although some patients have the condition longer than a year. Death, attributed to tuberculosis, has been reported in a few instances. A tuberculoid infiltrate of the myocardium was noted in one postmortem examination, a characteristic which Nickerson [36] reported in a case of frank sarcoidosis.

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40. Jordan, J. W., and Osborne, E. D.: Besnier-Boeck's Disease: Report of Two Cases of Extensive Involvement, Arch. Dermat. & Syph. **35**:663 (April) 1937.

41. Mellon, R. R., and Beinhauer, L. G.: The Pathogenesis of Noncaseating Tuberculosis of the Skin and Lymph Glands, Arch. Dermat. & Syph. **36**:515 (Sept.) 1937.

42. Pautrier, M.: Les lesions erythrodermiques pures de la maladie de Besnier-Boeck-Schaumann, Ann. de dermat. et syph. **6**:28, 1936.

ABSTRACT OF DISCUSSION

Dr. Earl D. Osborne, Buffalo: In the time at his disposal, Dr. Michelson has covered this subject thoroughly. There are some things which he did not have time to mention. During the past two years Dr. Jordan and I have had occasion to study several cases which we published under the name Besnier-Boeck disease. There were some striking findings which support the opinion of Dr. Michelson, that the condition is a generalized disease.

One of our patients, a boy, was particularly interesting. He had active pulmonary tuberculosis, with a positive reaction to tuberculin. Two years later when we saw the boy, the pulmonary condition was arrested and he had characteristic sarcoid lesions, with ocular involvement. Reactions to tuberculin were consistently negative for several years. Later he had virulent pulmonary tuberculosis with a positive reaction to tuberculin, during which all clinical evidence of activity of the sarcoid lesions disappeared.

From the etiologic standpoint, one cannot overlook the work of Sabin and her associates on the production of an epithelioid cell reaction by injection of certain fatty substances extracted from tubercle bacilli, hay bacilli and other organisms. All physicians are familiar also with the reports of conditions typical of extensive sarcoid or Besnier-Boeck disease or lymphogranuloma benignum of Schaumann which have been proved to be due to leprosy and syphilis. We feel, as Dr. Michelson does, that this condition may be produced by multiple agents, that it is a generalized disease and that each case requires complete and thorough study in order to determine the exact cause. This sometimes is extremely difficult. One of our cases has been under observation for about ten years. At one time, at a meeting of the Central States Dermatological Society, a diagnosis of extensive tuberculosis with cystic degeneration of the bones in the hands and feet was made. Hundreds of smears from the nose were made for lepra bacilli. At one time the patient was sent to Carville for complete study. No leprosy could be found. A large number of animal inoculations from glands in the skin had been made. So far we have been unable to determine the etiologic agent.

Dr. Fred Wise, New York: Can Dr. Michelson tell how frequent clinical parotitis is in comparison with sarcoid in general?

Dr. Lee McCarthy, Washington, D. C.: Before giving up the idea that tuberculosis has nothing to do with the causation of this disease one should consider certain facts. One is that 2 cases of lupus vulgaris of the face have recently been observed in which there were roentgenographic changes in the bones of the fingers identical with the changes seen in many cases of sarcoid. Secondly, it is difficult to discount entirely the careful work of Kyrle, who made biopsies daily for nineteen days in a case of sarcoid with young progressive lesions. At the end of ten days he found a typical picture of sarcoid and demonstrated large numbers of what were considered to be tubercle bacilli.

Dr. Clark W. Finnerud, Chicago: Although a good many cases of sarcoid have been thoroughly studied without definite evidence of tuberculosis having been found, a large number of cases have been reported as instances of sarcoid which have not been thoroughly studied. There seems to be less tendency now than formerly to regard the tubercle bacillus as the sole cause of this form of stimulation. It seems logical to assume that organisms, including tubercle bacilli, may be capable of producing toxins which may cause the systemic stimulation responsible for the symptoms. I think that dermatologists should be grateful for the work of Dr. Michelson. I am not familiar with it.

DR. FRED D. WEIDMAN, Philadelphia: It is not common practice to perform biopsies of material from the parotid gland or, for that matter, from the tonsil, and the authors' contribution today is due to the fact that they have resorted to that procedure. While the possibility may be remote, in differential diagnosis one must consider Mikulicz' disease, which causes swelling of the parotid glands and disease of the lacrimal glands. One should also remember the presentation last year of Beinhauer and Mellon (Pathogenesis of Noncaseating Tuberculosis of Skin and Lymph Glands, ARCH. DERMAT. & SYPH. **36**:515-533 [Sept.] 1937), in which they claimed that a particular stage in the life cycle of the tubercle bacillus is responsible for the condition which general pathologists call noncaseating tuberculosis and which dermatologists know as the sarcoid reaction.

DR. H. E. MICHELSON, Minneapolis: I hope I did not give the impression that I think tuberculosis has nothing to do with sarcoid. I merely stated that I think there are some cases of sarcoid in which tuberculosis cannot be proved to be present. There is no question in my mind that the lesions in many cases of Boeck's sarcoid have been other forms of tuberculosis, especially the lupus miliaris type. It has been my conviction for some time that one must not make a final classification of a lesion from examination of one or two biopsy slides, because repeated excisions must be made before one can be positive.

About 100 cases of uveoparotitis have been reported in the literature, and there are many cases of sarcoid with involvement of the lacrimal glands and with involvement of the iris. The Mikulicz syndrome is similar clinically to this condition but is usually due to leukemia or lymphosarcoma.

LOCAL ARTERIAL EMBOLISM FOLLOWING AN INTRAMUSCULAR INJECTION

ANDREW G. FRANKS, M.D.
NEW YORK

Although local arterial embolism is rather infrequent, it may occur during routine intramuscular syphilitic therapy. The after-effects of embolism are mostly mild, but they may sometimes include constitutional symptoms or interference with the patient's locomotion.

Cases of external popliteal paralysis,[1] sciatica,[2] gangrenous changes and destruction of the anastomoses of the gluteal and internal pudendal arteries, with destruction and gangrene of the rectum, bladder, genitals and thigh [3] are reported.

Freudenthal,[4] the first author to demonstrate the true nature of the condition, made a study of the cases by observation of tissue. Histologically he found suspended particles of bismuth subsalicylate in the deep cutaneous arteries. From this he concluded that the superficial cutaneous arteries were embolized and that all other changes were secondary to this phenomenon.

REPORT OF A CASE

J. D., an Italian man aged 39, entered the clinic on March 21, 1933, for antisyphilitic treatment. He complained of dizziness and headache and showed a positive Wassermann reaction of the blood. The disease was diagnosed as latent syphilis, and the patient received fifty-two injections of mapharsen, together with sixty-one injections of bismuth subsalicylate intramuscularly. After admission his spinal fluid was examined and was found normal. On Feb. 10, 1938, he received

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From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.

1. Gaté, J.; Cuilleret, P., and Chanial, G.: Dermite livédoïde et paralysie du sciatique, consécutives à une injection de bismuth, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Lyon) **44**:161-163 (Feb.) 1937.

2. Negrisoli, M. M.: Contributo allo studio delle embolie da bismuto a proposito di un caso di dermite livedoide con sciatalgia, Gior. ital. di dermat. e sif. **77**:657-667 (Aug.) 1936.

3. Payenneville and Castagnol: Quatre nouveaux cas de dermite livédoïde et gangréneuse de Nicolau à la suite d'injection de quinby, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **37**:1027-1034 (July) 1930.

4. Freudenthal, W.: Lokales embolisches Bismugenol-Exanthems, Arch. f. Dermat. u. Syph. **147**:155-160 (April) 1924.

his first and only injection of 1 cc. of iodobismitol with saligenin. The injection was given in the upper outer quadrant of the left buttock, through an ordinary needle for intramuscular injection. Aspiration was done as a routine with all intramuscular injections. The patient did not immediately show signs of discomfort and was not seen for seven days following the injection. He stated that he felt severe pain shortly after leaving the clinic and that blood flowed from the site for about an hour. The pain was mostly at the site of the injection and radiated down the thigh.

Examination of the left buttock revealed an irregularly shaped bluish red infiltrated plaque, with a superficial elevated and retiform triangular network of blood vessels, 2 inches (5 cm.) across the base and 1½ inches (4 cm.) along the sides. The eruption was still hot and painful on pressure. No deep infiltration could

Lesion following injection of iodobismitol with saligenin.

be felt. Movement of the thigh was unhindered. No other lesions were present on the thigh or buttock. The patient refused excision of tissue for histologic examination. Local treatment with wet dressings was instituted. The patient was seen again at the syphilitic clinic eleven days after the injection of iodobismitol with saligenin; there were no particular signs of discomfort. He was much improved; the infiltration had decreased. The eruption was still present, with the retiform network of blood vessels. On pressure the area was still hard, warm and tender to the touch. The patient was seen again twenty-one days after the injection. The erythema and retiform network had disappeared, and the infiltration was less, but the skin was slightly scaly, owing possibly to local wet dressings. No subjective symptoms were present. A few days later the patient was given bismuth subsalicylate again without ill effects. The eruption had completely disappeared.

Correspondence

FREI ANTIGEN PREPARED FROM MOUSE BRAIN

To the Editor:—In their statement (ARCH. DERMAT. & SYPH. **38**:383-388 [Sept.] 1938) that "the emulsion of mouse brain infected with the virus of lymphogranuloma venereum produced strongly positive reactions in all subjects known to have or have had lymphogranuloma venereum," Dr. Binkley and his associates have confirmed the results which Dr. Suskind and I [1] have already published on the use of Frei antigen prepared from mouse brain. Since May 1934 we have performed 463 Frei tests with mouse brain antigen on 173 lymphogranulomatous subjects. All of the reactions were positive. There is no doubt, then, that this antigen yields a positive reaction in lymphogranulomatous subjects.

Dr. Binkley and his associates further state that "in the control group of patients without lymphogranuloma, however, there was a high percentage of cases in which the emulsion of normal mouse brain produced a reaction." We have already observed this.[1] It is my purpose in this communication to emphasize the facts that (*a*) all papules resulting from the intradermal inoculation of mouse brain antigen cannot be interpreted as evidence of a positive reaction, and (*b*) the presence of reactions in control tests does not interfere with the specificity of the Frei test as performed with antigen prepared from mouse brain.

Any suspension of a foreign substance, particularly of tissue, when injected intradermally into a human subject will produce an inflammatory response at the site of inoculation. This response, which manifests itself in most normal subjects as a small papule independently of whether the inoculum is an emulsion of human pus or of mouse brain, must and can be differentiated from a positive Frei reaction. Such differentiation can be made only by measurement of the size of the papule. One must select a definite size, based on agreement with clinical findings, at and above which a reaction is classed as positive and below which it is classed as negative.

Frei [2] in the original description of his test stated that a positive reaction is manifested by an erythematous papule 0.75 to 1 cm. in diameter. Later investigators in the United States, using antigen prepared from human pus, have accepted as evidence of a positive reaction a papule whose diameter is not less than either 5 mm.[3] or 6 mm.[4] Smaller reactions are regarded as nonspecific.

Mouse brain antigen as used by me has been standardized so that 0.1 cc. used intradermally in lymphogranulomatous subjects produces an erythematous papule not less than 7 mm. in diameter and usually from 7 to 10 mm.[1] My colleagues and I have found in 823 control tests performed with antigen prepared from normal mouse brain on lymphogranulomatous and nonlymphogranulomatous subjects and

1. Grace, A. W., and Suskind, F. H.: The Use of Standardized Mouse Brain Antigen, J. A. M. A. **107**:1359 (Oct. 25) 1936.

2. Frei, W.: Eine neue Hautreaktion bei Lymphogranuloma inguinale, Klin. Wchnschr. **4**:2148 (Nov. 5) 1925.

3. Cole, H. N.: Lymphogranuloma Inguinale, the Fourth Venereal Disease, J. A. M. A. **101**:1069 (Sept. 30) 1933.

4. Peightal, T. C.: Pelvic Infection: Laboratory Aids in Diagnosis and Treatment, New York State J. Med. **36**:173 (Feb. 1) 1936.

with lymphogranulomatous mouse brain on normal subjects that a papule larger than 6 mm. in diameter was not produced and also that less than 6 per cent of the papules were as large as 6 mm. Dr. Binkley and his associates are therefore in error in reporting the control test papule 5 mm. in diameter produced with normal mouse brain (fig. 1*B*, their paper) as indicating a positive reaction. It indicates a negative reaction.

I am not familiar with any cutaneous test which will "produce clearcut reactions, as compared with definitely negative reactions to control tests." The pseudoreactions obtained in the Schick and Dick tests may be cited in this connection.[5]

I concur in, but cannot understand the significance of, the statement of Dr. Binkley and his associates that "any cutaneous test which . . . depends on the mathematical result obtained by subtracting the size of a control dermal papule from the size of a diagnostic dermal papule has a handicap which no other diagnostic intradermal test possesses." Nowhere in the literature on the use of mouse brain antigen is mention made of subtracting the size of a control papule from that of a test papule for any purpose, nor has Binkley made use of such a mathematical procedure in his study of this material.

I note that while the authors "undertook the clinical evaluation of mouse brain antigen with real enthusiasm" the portion of their review of the literature which deals with mouse material includes only papers by Strauss and Howard[6] and by Von Haam and Hartwell.[7] Favorable reports on the use of the material have been made by Von Haam and Hartwell,[7] Lichtenstein and Von Haam,[8] D'Aunoy and Von Haam,[9] Bacon[10] and Bloom.[11]

I feel that the following facts have been established in regard to Frei antigen prepared from mouse brain:

1. It uniformly yields a positive reaction in lymphogranulomatous subjects.

2. Nonspecific reactions occur as with antigens prepared from human pus and as with materials used for other cutaneous tests.

3. It is possible to differentiate nonspecific from positive reactions on the basis of the size of the papule.

4. Frei antigen prepared from mouse brain has been standardized so that the largest nonspecific papule is smaller than the smallest papule indicating a true positive reaction.

ARTHUR W. GRACE, M.D., New York.

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5. Topley, W. W. C., and Wilson, G. S.: The Principles of Bacteriology and Immunity, Baltimore, William Wood & Company, 1937, pp. 1082 and 1162.

6. Strauss, M. J., and Howard, M. E.: Frei Test for Lymphogranuloma Inguinale: Experiences with Antigens Made from Mouse Brain, J. A. M. A. **106**:517 (Feb. 15) 1936.

7. von Haam, E., and Hartwell, R.: Value of Mouse Brain Antigen for the Diagnosis of Lymphogranuloma Inguinale, Proc. Soc. Exper. Biol. & Med. **36**:269 (April) 1937.

8. Lichtenstein, L., and von Haam, E.: Usefulness of Organ Emulsions of Infected Animals in the Diagnosis of Lymphogranuloma Inguinale, Proc. Soc. Exper. Biol. & Med. **32**:952 (March) 1935.

9. D'Aunoy, R., and von Haam, E.: The Virus of Lymphogranuloma Inguinale, South. M. J. **9**:911 (Sept.) 1936.

10. Bacon, H. E.: The Specificity of the Frei Test in Lymphopathia Venera, Am. J. Digest. Dis. & Nutrition **2**:570 (Nov.) 1935.

11. Bloom, D.: Lymphogranuloma Venereum: The Present Status, New York State J. Med. **38**:616 (April 15) 1938.

NITRITOID REACTION FOLLOWING AN INJECTION OF TRYPARSAMIDE

To the Editor:—I wish to comment on the recent report of Drs. G. D. Astrachan and A. G. Franks (ARCH. DERMAT. & SYPH. **38**:949 [Dec.] 1938).

These authors stated that only 2 cases of nitritoid reaction following an injection of tryparsamide have been reported. In the *British Journal of Venereal Diseases* (**10**:99 [April] 1934) I briefly reported a case of severe nitritoid reactions to tryparsamide. I observed a second case of such reactions in my private practice in 1936. This case has been reported in the Queries and Minor Notes of *The Journal of the American Medical Association* (**106**:1224 [April 4] 1936). At the present time I have under my care in the syphilis clinic of the Royal Victoria Hospital a third patient who has suffered from typical nitritoid reactions.

FRANK E. CORMIA, M.D., Montreal, Canada.

News and Comment

MEDAL TO PROFESSOR PAUTRIER

A committee of colleagues, friends and pupils of Prof. L. M. Pautrier will present him with a medal on May 14, 1939, in honor of his twenty years of teaching in Strasbourg, France. The cost of the medal is 100 francs. Subscriptions are to be sent as soon as possible to Dr. Frederic Waringer, Clinique Dermatologique, Strasbourg, France.

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

PAGET'S DISEASE OF THE SKIN AND ITS RELATION TO CARCINOMA OF THE APOCRINE SWEAT GLANDS. H. A. WEINER, Am. J. Cancer **31**:373 (Nov.) 1937.

The author reports the clinical, postmortem and histologic observations in a case of adenocarcinoma of the vulva with Paget's disease of the overlying skin. The original findings and views of Jacobaeus and Muir are reported in support of the contention that the Paget cell is a cancer cell resulting from intraepidermal metastases of an overlying carcinoma of adenomatous type. The author believes the latter to be a cancer of the apocrine sweat glands and states that true Paget's disease always has its origin in the breast, the axilla or the anogenital region. Fifty-seven reported cases of supposed extramammary Paget's disease are briefly reviewed, and only 26 of these are accepted by the reviewer as examples of this disease.

KAPOSI'S SARCOMA. D. S. D. JESSUP, Am. J. Cancer **31**:556 (Dec.) 1937.

The case reported was unusual in that the manifestations were limited to two nodules on the forehead and scalp and had been diagnosed before histologic study as basal cell epithelioma. The lesions recurred twice after excision and were unresponsive to irradiation.

CONGENITAL XANTHOMA TUBEROSUM. H. CHARACHE, Am. J. Cancer **31**:563 (Dec.) 1937.

The author reports a case of xanthoma tuberosum in a baby. The lesion developed at a site of trauma and in the absence of cholesteremia. The histologic sections showed an abundance of giant cells but no xanthoma cells.

"INFLAMMATORY CARCINOMA" OF THE BREAST. GRANTLEY W. TAYLOR and ADOLPH MELTZER, Am. J. Cancer **33**:33 (May) 1938.

"Inflammatory" or "erysipeloid" carcinoma of the breast is reported as a subepidermal carcinomatous lymphatic permeation in which inflammatory reaction with round cell infiltration is due chiefly to blockage of the lymphatic vessels. Thirty-eight cases are reported from the Pondville Hospital, Wrentham, Mass., with an average duration of life of less than two years. Roentgen therapy produced the best palliative results, and surgical treatment was found to be useless.

THE RELATIONSHIP OF MALIGNANT AMELANOTIC MELANOMA TO EXTRAMAMMARY PAGET'S DISEASE. ARTHUR P. STOUT, Am. J. Cancer **33**:196 (June) 1938.

A case of pigment-free melanoma in the popliteal region, the primary manifestation of which was indistinguishable from Paget's disease, is reported and differentiated from the latter. The author states that true Paget's disease is confined to the mammary, axillary and anogenital regions and that an apparently similar lesion elsewhere is probably a slowly growing amelanotic melanoma, especially if it develops at the site of a preexisting lesion. Unless there is pigment formation or the cells are dopa positive, it may be impossible to distinguish between the Paget cell of the epidermis and the cells of malignant melanoma, although metastases from melanoma usually assume a cordiform arrangement, the nevoid cells being separated by fibrous strands.

CARCINOSARCOMA. O. SAPHIR and A. VOSS, Am. J. Cancer **33**:331 (July) 1938.

The authors investigated 153 reported cases of carcinosarcoma but failed to agree with that diagnosis in all but 4. Squamous cell carcinoma with transitional features, marked anaplasia of carcinoma cells, associated chronic inflammation with round cell infiltration and sarcoma invaded by normal or metaplastic epithelial structures may be mistaken for carcinosarcoma.

LEIOMYOMA OF THE ORAL CAVITY. ARTHUR P. STOUT, Am. J. Cancer **34**:31 (Sept.) 1938.

The author reports 2 cases of leiomyoma of the oral cavity. The growths were situated at the base and on the dorsum of the tongue as soft pedunculated tumors. He comments on the rarity of this condition because of the absence of smooth muscle fibers in most of the oral cavity and expresses the opinion that one lesion apparently originated in a circumvallate papilla and the other from the smooth muscle of a blood vessel.

FOERSTER, Milwaukee.

XERODERMA PIGMENTOSUM WITH MENTAL DEFICIENCY: REPORT OF TWO CASES. A. G. SILBERSTEIN, Am. J. Dis. Child. **55**:784 (April) 1938.

The author reports 2 cases of xeroderma pigmentosum in brothers. There were associated mental deficiency, abnormality of speech and gait and moderate somatic underdevelopment. There was a possibility of degeneration of the central nervous system analogous to the degenerative lesions of the skin.

MELORHEOSTOSIS LÉRI. J. B. GILLESPIE and J. A. SIEGLING, Am. J. Dis. Child. **55**:1273 (June) 1938.

This condition, which can be recognized only roentgenologically, is characterized by dense cortical hyperostosis causing an enlargement of the affected part and extending in a linear streak along the bones of an extremity into some of the tarsal or carpal bones.

Its interest to the dermatologist is that in 3 of some 36 reported cases associated unilateral scleroderma affected the involved skin over the abnormal bones.

NELSON PAUL ANDERSON, Los Angeles.

VALUE OF IRRADIATED ERGOSTEROL IN THE TREATMENT OF ACNE VULGARIS. J. HINRICHSEN and A. C. IVY, Illinois M. J. **74**:85 (July) 1938.

The effects of viosterol (irradiated ergosterol) in the treatment of acne vulgaris were studied in 210 patients. The authors conclude that a definite and practical improvement may be obtained with daily administration of from 20,000 to 30,000 units of viosterol in about 20 per cent of patients with acne vulgaris after from two to eight weeks. Approximately 30 per cent of those who fail to show a practical improvement on this dose will do so on 100,000 units daily. This high dose should be accompanied by determinations of the serum calcium. The results indicate that viosterol is by no means specific in the treatment of acne.

BARBOUR, Peoria, Ill. [AM. J. DIS. CHILD.]

IDE TEST FOR SYPHILIS. C. R. REIN and C. E. HAZAY, J. Lab. & Clin. Med. **23**:954 (June) 1938.

This paper is a report on a comparative study of the Ide test described by S. and T. Ide (*Jap. J. Dermat. & Urol.* **39**:152 [Feb.] 1936; abstracted, ARCH. DERMAT. & SYPH. **35**:306 [Feb.] 1937), and the Kline heated serum tests and the complement fixation methods, with clinical evaluation in more than 1,000 cases. In this study the technic of the Ide test was modified by employing only inactivated serum and utilizing the paraffin ring slides described for the Kline heated serum test.

The results showed the modified Ide test to be somewhat less sensitive and less specific than the Kline heated serum tests and the complement fixation methods. The Ide test is simple and easily performed. With a commercially prepared antigen it gave results considerably less sensitive than those obtained with antigen supplied by Dr. Ide.

GRAUER, New York.

PEDICULOSIS IN RATS KEPT ON A RIBOFLAVIN-DEFICIENT DIET. P. GYÖRGY, Proc. Soc. Exper. Biol. & Med. **38**:383 (April) 1938.

In an extensive study of the vitamin B_2 complex in 2,000 animals given diets deficient in vitamin B_6 and 600 rats reared on diets deficient in riboflavin, György observed that pediculosis developed in about 20 per cent of the animals kept on the riboflavin-free diet for from eight to ten weeks but not in the other animals. Somewhat remarkable also is the fact that therapeutic administration of riboflavin was followed not only by growth of the rats but by complete disappearance of the pediculi, often accompanied by replacement of the diseased patches by new fur.

HANSEN, Minneapolis. [AM. J. DIS. CHILD.]

PRECANCEROUS SKIN CHANGES. J. W. ORR, J. Path. & Bact. **46**:495, 1938.

An investigation has been made of the changes in the skin of white mice treated with six carcinogenic hydrocarbons, ten noncarcinogenic hydrocarbons of related chemical structure and a group of unrelated irritants. These substances have been used in solution in benzene and acetone, the latter solvent being of greater value for the present purpose, as it is without effect on normal mouse skin. Early epilation is a striking feature of the action of cholanthrene, methylcholanthrene, 3,4-benzpyrene and 1,2,4,6-dibenzanthracene but not of 1,2,5,6-dibenzacridine and 3,4-benzphenanthrene. It occurs with some noncarcinogenic hydrocarbons but to a much less extent than with the four most potent carcinogens. After epilation by a carcinogen, the regenerated hair is abnormal. The appearance of tumors is preceded by progressive thickening and loss of elasticity and by passive congestion of the skin. Ulceration of the surface does not bear any relation to tumor formation. Histologically, the carcinogens produce squamous hyperplasia of the epidermis in the first weeks of treatment. Thereafter, the progressive changes are found in the deeper tissues, and the most significant phenomena are: (1) transformation of the collagen of the superficial, and later of the whole, dermis into a fine-fibered, nonrefractile type; (2) passive congestion of the subcutis; (3) alterations in the texture of the elastic tissue without necessarily an increase in its amount, and (4) absence of inflammatory cell infiltration. When tumors appear, they are frequently related to fibrous scars in the subcutis, to the gaps in the elastic tissue of the dermis or to both. In comparing the carcinogens it was observed that the rate of progress of the changes cited corresponds with the rapidity with which tumors are induced. Similarly, mice in which tumors appear early or late are those in which these changes advance rapidly or slowly, respectively. When comparable changes occur with noncarcinogenic applications, evidence of inflammation is usually present. It is suggested that the cancerization of the epithelial cells by the carcinogenic hydrocarbons is at any rate partly the result of the changes in the deeper tissues and that its mechanism may be related to the consequent interference with their nutrition.

FROM AUTHOR'S SUMMARY. [ARCH. PATH.]

BRIEF NOTES ON CYSTICERCOSIS AND LUETIC PSEUDOCYSTICERCOSIS. ALDO CASTELLANI and G. ACANFORA, J. Trop. Med. **41**:213 (July 1) 1938.

The authors compared syphilitic pseudocysticercosis and cysticercosis. Cysticercosis (infection with larvae of Taenia solium, the tapeworm of pork) occurs rarely in man. Three clinical varieties were recognized: (1) the subcutaneous and muscular, (2) that of the central nervous system and (3) the ocular.

In the first type the cysticerci are palpable as pea-sized subcutaneous nodules. The lesions are usually painless and are found on the extremities. The diagnosis is made by excision and examination of the nodules, with demonstration of the parasite. There is no specific treatment.

Syphilitic pseudocysticercosis is characterized by similar nodules under the skin of the arms and legs. The diagnosis is made by histologic examination, which shows fibrosis without Trichinella larvae. The Wassermann test is positive, and the nodules disappear under the influence of antisyphilitic therapy.

LAYMON, Minneapolis.

TREATMENT OF INFECTED WOUNDS WITH UREA. L. F. MULDAVIN and J. M. HOLTZMANN, Lancet **1**:549 (March 5) 1938.

Muldavin and Holtzmann report the results of treatment of infected wounds with urea in a series of 170 cases. The results were so encouraging that the adoption of this method of treatment as a routine in the casualty department of the Royal Free Hospital is under consideration.

The advantages of the treatment are: (1) It is cheap; (2) it produces no dermatitis; (3) it deodorizes foul-smelling wounds; (4) it dissolves necrotic material; (5) local circulatory conditions are improved; (6) it has no toxic effect, and (7) it has been successful when other treatments have failed.

Its disadvantages are: (1) It sometimes causes pain, and (2) it does not stimulate epithelization.

CAUSATION AND TREATMENT OF DERMATITIS. R. HALLAM, Lancet **1**:1259 (June 4) 1938.

Recognizing the important roles which low grade physical and mental resistance may play in dermatitis the author suggests the following simple classification of dermatitis: (1) traumatic dermatitis, (2) atopic dermatitis (infantile eczema and sequelae) and (3) sensitization dermatitis (often referred to as eczema).

Traumatic dermatitis is an inflammatory reaction of the skin following application of an external irritant. Primarily, traumatic dermatitis is limited to the area of skin which has been in contact with the particular irritant, whereas sensitization dermatitis tends to spread and involve even distant areas.

Eczema, often classified as a sensitization dermatitis, has not been satisfactorily explained. The multiplicity of the occasional causes suggests that it is a syndrome and not a morbid entity, the predisposition being the common factor.

Infantile eczema is now commonly regarded as an entity and distinguished from other eczemas. It is often referred to as atopic dermatitis. In a considerable proportion of cases, if not in all, there is familial disposition.

The method of distinguishing between the various types of dermatitis depends in large measure on the taking of a thorough, discriminate history.

As far as treatment is concerned, elimination of the cause, rest and protection are applicable to all the patients.

In infantile dermatitis zinc oxide and kaolin lotion are advocated in place of soap and water in cleansing of the skin.

THE NATURAL HISTORY OF STRAWBERRY NEVI. W. A. LISTER, Lancet **1**:1429 (June 25) 1938.

From a review of the literature and a study of a series of cases it appears that strawberry nevi of infants have a natural history entirely different from that of any other type. The essential point of distinction is that they enjoy more or less rapid growth during the first few months (never over a year) after their appearance. Then retrogression sets in, and they disappear of their own accord, on the average about the fifth year of life.

It follows that drastic measures for the destruction of these nevi are inadvisable, and treatment should be expectant and conservative.

LANGMANN, New York. [AM. J. DIS. CHILD.]

VARIETIES OF CARCINOMA OF THE UPPER LIP. J. DELARUE AND C. FAYEIN, Bull. Assoc. franç. p. l'étude du cancer **27**:8, 1938.

Since 1922 carcinoma of the upper lip has been seen in 32 patients at the Cancer Institute of the Faculty of Medicine, in Paris. In 18 of these the growth originated in the cutaneous part of the lip; in 3 it grew from the adjacent skin into the lip. In all except 1 with a spinocellular carcinoma, which metastasized to the lymph nodes, the carcinomatous growth responded well to roentgen therapy. In 5 instances the carcinoma developed from the mucous membrane, and in 6 it straddled the mucocutaneous junction. This type showed more marked histologic irrgularities than the cutaneous type; in most of these instances the carcinoma metastasized to submaxillary lymph nodes; in a certain instance it metastasized also to the preauricular lymph node on the side of the tumor. Carcinoma of the upper lip originating from the skin behaved like cancer of the face in general. It was not related to sex. Metastases were rare; local roentgen therapy was highly successful. The prognosis in such cases is good. Carcinoma of the mucosa behaved like cancer of the buccal mucosa. It was more common in man (11 cases in a series of 12). It grew and metastasized rapidly. The rarity of carcinoma of the upper lip is evidenced by the fact that in the period during which 200 cases of carcinoma originating from the mucous membrane of the lower lip were observed only 11 cases were encountered in which it originated from the lower lip.

I. DAVIDSOHN. [ARCH. PATH.]

LATE CUTANEOUS LESIONS FOLLOWING SUBCUTANEOUS INJECTIONS OF THORIUM X. R. J. WEISSENBACH, Bull. Soc. franç. de dermat. et syph. **45**:50 (Jan.) 1938.

The author observed three types of lesions following the subcutaneous injection of thorium X in a woman aged 56: (1) a plaque of atrophic radiodermatitis with telangiectases, (2) a plaque of fibrous radiodermatitis with calcification and (3) a necrotic ulcer.

The patient had been treated with thorium X for chronic arthritis from December 1930 to February 1931. She had received nine injections in the thighs, totaling 2,200 micrograms. She stated that the radiodermatitis began insidiously two or three years after the injections.

Weissenbach stated that single doses of thorium X should not exceed 150 micrograms, that the injections should be given intramuscularly rather than superficially and that treatments should never be given near the sites of acute or chronic inflammatory processes.

LIPIDEMIA AND CHOLESTEREMIA IN PSORIATIC PATIENTS WITH OR WITHOUT ARTHRITIS. R. J. WEISSENBACH, J. MARTINEAU and G. BOUWENS, Bull. Soc. franç de dermat. et syph. **45**:57 (Jan.) 1938.

The discordant results of previous studies by various investigators prompted the authors to investigate further the role of lipoids in psoriasis. In the cases studied the lipoid and cholesterol values of the blood were similar to those of normal subjects. In some instances the amounts were below normal. The lowering of the lipoid content of the blood seemed to coincide with new outbreaks of psoriasis on the skin or articular flare-ups in cases of arthropathic psoriasis. The authors were unable to confirm the opinion of Grütz and Bürger that psoriatic patients regularly showed increased lipoid in the blood. They concluded that if a person with psoriasis presented an increased lipoid content causes other than the psoriasis should be investigated.

VERRUCOUS LICHENIFIED AURIDES IN ISOLATED NODULES AND VEGETATING PLAQUES. L. M. PAUTRIER and J. ROEDERER, Bull. Soc. franç. de dermat. et syph. **45**:139 (Feb.) 1938.

The authors call attention to an unusual cutaneous reaction to chrysotherapy characterized by verrucous nodules and lichenified plaques. The eruption

resembled a mixture of lichen planus and verrucous lichenification and occurred in a woman aged 44 who received gold therapy for arthritis. Treatment was begun in October 1933, and the eruption was noted in March 1934, after she had received about thirty injections of a gold preparation (name of product and dose not known). The cutaneous lesions were located on the sides of the neck, trunk and extremities, and there were white patches and tiny erosions on the buccal mucosa. The color of the eruption varied from wine red to brown. After the application of various drugs the lesions finally began to involute early in August 1934, and by October no trace of them remained except pigmentation.

The histologic features of an early papule were consistent with a diagnosis of lichen planus, while an older verrucous plaque showed verrucous lichenification without signs of lichen planus. The authors concluded that the gold salt precipitated true lichen planus followed by verrucous lichenification due to prolonged scratching.

ACUTE LUPUS ERYTHEMATOSUS WITH DEATH IN FIVE DAYS. J. ROUSSET and J. RACOUCHOT, Bull. Soc. franç. de dermat. et syph. **45**:190 (March) 1938.

The authors report a case of exanthematic lupus erythematosus in a man aged 39. The patient was brought to the clinic in an extremely grave condition on May 29, 1937. There were intense stomatitis and an erythematosquamous eruption on the face and neck, the backs of the hands, the scrotum and the perianal region. For two or three months the patient had presented scaly lesions on the face. Shortly before the onset of the acute symptoms the patient was given a series of intravenous injections of cyanide of mercury. . After the third injection the stomatitis and intoxication appeared.

The authors expressed the belief that the administration of the medication and the onset of lupus erythematosus were coincidental. Death occurred in five days; an autopsy was done, and no signs of mercurial poisoning were found. There were no signs of tuberculosis.

KERATOCONJUNCTIVITIS OF MOLLUSCUM CONTAGIOSUM. TZANCK, OFFRET and DUPERRAT, Bull. Soc. franç. de dermat. et syph. **45**:261 (Feb.) 1938.

The authors report a case of severe follicular conjunctivitis of the right eye in a man aged 32 who had molluscum contagiosum of the lower lid. The condition, of four months' duration, disappeared after removal of the molluscum contagiosum. Such conjunctivitis was first described by Elsching, of Prague, Czechoslovakia, in 1897, and many other publications on the subject have since appeared. The conjunctivitis of molluscum contagiosum simulates trachoma. It is thought by some authors to be directly caused by the filtrable virus which is responsible for the cutaneous lesions. Other observers believe it to be on a "reflex" basis, while still others think it is due to sensitization to the infectious agent.

Adenitis is a prominent symptom. Elsching in 1922 stated that among 10,000 patients examined annually in his clinic an average of 4 with ocular complications of molluscum were seen.

ANTISYPHILITIC TREATMENT FOR SCLERODERMA. LESZCZYNSKI, Bull. Soc. franç. de dermat. et syph. **45**:380 (Feb.) 1938.

The author stated the following opinions based on his personal observations: 1. Scleroderma has its origin in disturbances of the endocrine glands. 2. Syphilis may indirectly cause scleroderma by provoking a chronic interstitial inflammation of these glands. 3. Circumscribed scleroderma, anetoderma of Jadassohn and poikiloderma of Jacobi and possibly striae distensae possess a unity of pathogenesis.

In accordance with his belief that scleroderma is frequently associated with syphilis of long standing, he prescribed bismuth therapy as a routine, adding arsenicals in cases in which the serologic tests for syphilis were positive.

KAPOSI'S DISEASE LOCALIZED ON PALM. GOUGEROT and BURNIER, Bull. Soc. franç. de dermat. et syph. **45**:387 (March) 1938.

The authors describe the case of a man aged 40. The nodular lesions, which were of three months' duration, affected only the palms. There was neither hemorrhage nor pigmentation. The histologic picture was consistent with a diagnosis of nonhemorrhagic Kaposi's disease. LAYMON, Minneapolis.

MASONS' ECZEMA (AN EXPERIMENTAL AND CLINICAL STUDY OF THE ECZEMA QUESTION). WALTER BURCKHARDT, Arch. f. Dermat. u. Syph. **178**:1, 1938.

The author studied 80 patients with brick masons' eczema and 100 control patients with normal skins, by means of patch tests with cement, lime, calcium hydroxide, dicalcium and tricalcium silicate and aluminate. Only 10 per cent of the patients with eczema showed allergic hypersensitiveness. The other 90 per cent and all the controls showed microscopic and macroscopic eczematoid dermatitis, which was considered a banal toxic reaction. The eczematous reaction of the patients with masons' ezema was attributed to delayed neutralization of the alkalis, with a resulting toxic reaction rather than an allergic response. The early lesions of masons' eczema correspond to the reaction seen on normal skin. Repeated exposure to large amounts of the materials results in the picture of chronic eczema, clinically and microscopically. The author concludes that the history and clinical picture are more important for the diagnosis of masons' eczema than are positive results from patch tests. Protection of the skin against massive contact with cement and lime is recommended.

HISTOPATHOLOGY OF OSLER'S DISEASE (HEREDITARY HEMORRHAGIC TELANGIECTASIA). A. FINGERLAND and B. JANOUSEK, Arch. f. Dermat. u. Syph. **178**:54, 1938.

The author reports the case of a woman aged *27*, who suffered from frequent profuse epistaxis from early youth up to the age of *22*. Numerous telangiectatic lesions were present on the forearm and soft palate. Ten of the patient's relatives suffered from nosebleed. Microscopic examination revealed papillary telangiectasis. The dilated vessels occasionally showed thrombosis and hyaline degeneration, with hemorrhage into the surrounding tissue. The collagenous and elastic tissue were normal. The walls of the venules were thickened, owing to noninflammatory increase of the muscle cells or adventitial cells. The author concludes that such thickening narrows the lumen, increases the pressure in the capillaries and results in capillary dilatation.

ACQUIRED EPIDERMOLYSIS BULLOSA ASSOCIATED WITH CUTANEOUS AMYLOIDOSIS. ALFRED MARCHIONINI, Arch. f. Dermat. u. Syph. **178**:65, 1938.

A man aged 63, with lichenoid and poikiloderma-like cutaneous amyloidosis, had bullae on the dorsal surface of the feet after trauma. The author considers the condition to be acquired epidermolysis bullosa occurring as a result of decreased nutrition and resistance produced by damage to the cutaneous vessels by the amyloid infiltration and varicose veins.

SARCOID-LIKE CUTANEOUS TUBERCULOSIS CAUSED BY THE BACILLUS OF AVIAN TUBERCULOSIS. NIELS DANBOLT and ANTON BRANDT, Arch. f. Dermat. u. Syph. **178**:76, 1938.

A woman aged 50 presented generalized sarcoid-like lesions, especially of the face, with changes in the lungs, fingers and toes typical of those associated with Boeck's sarcoid. The reaction to old tuberculin was weakly positive, but that to avian tuberculin was definitely positive. Avian tubercle bacilli were cultured directly from the lesions, and positive inoculation was obtained in rabbits and chickens, but results were negative in guinea pigs. Six cases of Boeck's sarcoid

were studied by the same technic, with negative results. Human tubercle bacilli were isolated in 33 cases of lupus vulgaris. Investigation of tuberculous swine from the neighborhood showed 80 per cent with avian, 17.5 per cent with human and 2.5 per cent with bovine tuberculosis. There was thus an opportunity for human infection. The authors call the condition sarcoid-like tuberculosis, since they do not consider sarcoid tuberculous.

INVESTIGATIONS ON THE INFLUENCING OF INFLAMMATORY PROCESSES IN THE SKIN. D. CARRIE, Arch. f. Dermat. u. Syph. **178**:92, 1938.

One ear of a rabbit was exposed to ultraviolet rays, and the other was treated with anthralin (dihydroxyanthranol) ointment, with production of erythema in both instances. When tyrosine was added to the fodder, the erythema on both ears was intensified and prolonged. Addition of extract of adrenal cortex to the food tended to decrease the intensity of the erythema and shorten the duration. Administration of adrenal cortex extract to guinea pigs sensitized to dinitrochlorbenzene lessened the duration and intensity of reaction of the skin to subsequent application of the substance but had no effect on the allergy itself, as manifested by prolongation and intensification of the reactions after discontinuance of the extract.

BECKER, Chicago.

RELATIONS BETWEEN THE VIRUS OF PEMPHIGUS AND THAT OF RABIES. E. SCHWEINBURG and S. WOLFRAM, Ztschr. f. Immunitätsforsch. u. exper. Therap. **91**:341, 1937.

The serum of patients with pemphigus and that of rabbits that had been immunized with the virus of pemphigus were mixed with fixed virus and kept in the ice box for twenty-four hours, after which the mixtures were inoculated intracerebrally into guinea pigs. A large majority of the animals remained alive, as compared with the control animals, which had been inoculated with mixtures of fixed virus and normal rabbit or human serum or saline solution. Rabic immune serum mixed with the virus of pemphigus was kept at 0 C. for twenty-four hours and then injected subdurally into rabbits. Marked protection was observed. Rabbits immunized against pemphigus showed only slight resistance against rabies, while those immunized against rabies were protected against the virus of pemphigus to a higher degree.

USE OF IMMUNE SERUM IN THE TREATMENT OF ANTHRAX IN BULGARIA. P. KOSCHUCHAROFF, Ztschr. f. Immunitätsforsch. u. exper. Therap. **92**:53, 1938.

Among a population of about 6,000,000, there occur from 800 to 1,100 cases of anthrax. From 2,000 to 3,000 cases occur in domestic animals. The infection is contracted almost without exception by contact with diseased animals. The report is based on 521 cases in man. In each case the malignant pustule was characteristic, and bacteriologic studies were superfluous. In most cases it was located on the exposed parts (face, arms, legs), but no part of the body was free. The mortality was greater among those who had the primary lesion on the face. After a historical review of surgical and chemical therapy, the author presents the great success of serum therapy. The administration of large doses led to improvement in results, the mortality dropping from 33 per cent in 1912, with average doses of from 30 to 150 cc., to 3 per cent in 1935 and 1936, with larger average doses, reaching in some cases 1,500 cc. The methods of producing immune serum are reviewed. It is emphasized that no satisfactory method of standardization of anthrax immune serum is available and that normal serum is often just as efficacious as immune serum. I. DAVIDSOHN. [ARCH. PATH.]

Society Transactions

LOS ANGELES AND SAN FRANCISCO DERMATOLOGICAL SOCIETIES

KENDAL FROST, M.D., *Chairman*

Joint Meeting, Los Angeles, May 10, 1938

CHARLES R. CASKEY, M.D., *Acting Secretary*

A Case for Diagnosis. Presented by DR. IRVING R. BANCROFT and DR. KATHERINE MACEACHERN (by invitation).

E. C., an American woman aged 63, came to the hospital this morning and has not been studied completely. She was in this hospital a year ago, with a condition diagnosed as lymphatic leukemia. She subsequently had high voltage roentgen therapy, the amounts and dates of which are not known. Her present condition has existed about three weeks.

DISCUSSION

DR. UDO J. WILE, Ann Arbor, Mich. (by invitation): In view of the toxic condition, I am impressed with the possibility of hemorrhagic smallpox. The confluent hemorrhagic lesions, not only on the arm but in the mouth and on the forehead and both palms, are suggestive. Would it not be well to find out whether this patient has had any contact with smallpox and whether she has been vaccinated?

DR. WILLIAM H. GOECKERMAN: I think this picture would fit in with acute lymphatic leukemia. I am basing that largely on the large bullous lesions on the chest. It could be herpes zoster, but I think there is too much infiltration in the lesions. The eruption is compatible with lymphoblastoma. Microscopic study will have to settle the diagnosis.

DR. KENDAL FROST: In the hospital I have occasionally seen herpes zoster with a varicella-like generalized eruption. This patient's eruption is more extensive than any I have hitherto seen with that condition.

DR. MERLIN TREVOR-ROPER MAYNARD, San Jose, Calif.: It may be that the cell count was reduced so low that the patient is simply undergoing generalized changes of erythema multiforme with necrosis, such as appear after too intensive irradiation, when the blood count no longer responds.

DR. SAMUEL AYRES JR.: With the distribution of the eruption I do not see how one can get away from a diagnosis of herpes zoster. One must consider whether the leukemia caused the herpes zoster or the zoster was aggravated by the leukemia. I think from the clinical point of view, as far as the lesion on the arm is concerned, a diagnosis of herpes zoster cannot be escaped.

Keratosis Follicularis (Darier). Presented by DR. STANLEY CHAMBERS and DR. STANLEY ANDERSON.

R. E., a white American man aged 59, has cutaneous lesions which appeared six years ago and were first noticed on the inner aspects of the thighs. Similar lesions have since appeared, progressively, in the following areas: forearms, arms, back, chest, face, neck, scalp, palms and soles. Two years after the onset the patient noticed some of the areas becoming moist and verrucous. Careful examination

revealed that the elementary lesion was a small flesh-colored follicular papule. Other papules were larger and more keratotic. On the lower parts of the legs the hypertrophied follicular papules have coalesced to form large patches. In these areas superficial ulceration, weeping and extensive vegetation have occurred. Other areas, such as the upper part of the back and the extensor surfaces of the forearms and thighs, show coalescence of papules with eczematous characteristics. The tongue shows atrophic glossitis but no lesions described as characteristic of this disease. The histologic section was taken from the right shoulder. It showed marked hyperkeratosis, invagination of the epithelium and horny plugs. There was finger-like proliferation of the rete cones around the horny plugs, with marked dyskeratosis. In the dyskeratotic areas there was marked variation in the appearance of the degenerated epithelial cells. The histologic characteristics were consistent with those of Darier's disease.

Keratosis Follicularis (Darier). Presented by DR. A. F. HALL JR.

P. B. is a white girl aged 16. Her mother is said to have had flat wartlike lesions on her neck all her life. The patient had no nails or hair at birth. Her skin has always been dry. The present cutaneous disease began at the age of 6 years as small brown warty lesions on the neck. During the past year the lesions have become more generalized, practically covering the exposed portions of her neck, chest and back. About six months ago scattered lesions appeared on the abdomen and lately in the axillas. Moist plaques with a tendency to fissuring have been present on the inner aspects of the upper parts of the thighs for six or eight months.

When she was first examined the aforementioned areas were studded with follicular keratotic papules. On the chest, shoulders and back closely studded areas of papules showed crusting. The upper inner aspect of each thigh showed a palm-sized slightly raised moist plaque, with fissures along the lines of cleavage.

A histologic section showed hyperkeratosis of the orifices of the sebaceous and sweat ducts. A diagnosis of Darier's disease was made from the section.

Ultraviolet irradiation was given at the clinic, but made the condition worse. Several roentgen treatments brought about some improvement in places. During the past two months weekly applications of solid carbon dioxide have been given, and the areas treated show definite improvement.

DISCUSSION OF CASES OF KERATOSIS FOLLICULARIS

DR. WILLIAM H. GOECKERMAN: I believe the girl has typical Darier's disease, my only doubt being whether one could show that the mother had Darier's disease. According to the history, she has had these lesions confined to the area on the chest for a long time. The lesions in the early stages could show this picture, but I have never seen anything like it. I have seen patients whose history pointed rather strongly to a familial factor in this condition.

DR. UDO J. WILE, Ann Arbor, Mich. (by invitation): I was much interested in the man's condition. I do not believe I have ever seen a more extensive involvement. In most cases in this country the disease is much milder than in this one. I believe that this picture, however, corresponds much more closely to what Darier originally described under the name of psorospermosis follicularis vegetans. In other words, a vegetative factor was the distinguishing feature of the cases described by Darier, and this has not been so marked in the cases that have been observed and described in this country.

DR. KENDAL FROST: One of the cases I reported in 1935 was that of a Mexican woman, with vegetative lesions similar to those presented by this man. The mucosal lesions of this disorder are always interesting. I examined the mouth of the girl's mother and found some lesions on the roof which were suggestive, although they might have been caused by irritation from her dental plate.

Chronic Allergic Dermatitis Simulating Mycosis Fungoides. Presented by Dr. H. C. L. Lindsay.

Mrs. H. L., a white woman aged 41, states that she has had cutaneous trouble of an eczematous nature all her life. During the past three years this has been accentuated. Three different phases have been observed, namely, pemphigoid, exfoliative dermatitis, eczematoid thickening and pigmentation. There is marked allergic reaction to many different antigens. The patient is frail, nervous and underweight. She is blind from cataracts. At present her skin shows brownish pigmentation in many areas, most marked on the neck and arms. On the flexor surfaces of the forearms are several granulomas, resembling those resulting from iodides and bromides. Some of these show weeping and excoriated spots. There is no lymphatic enlargement. Laboratory tests have not shown any abnormality.

Her treatment has been with pancreatic extract internally and lotions, ointments and roentgen rays externally. She shows no improvement; however, she has recovered some vision in one eye.

DISCUSSION

Dr. Udo J. Wile, Ann Arbor, Mich. (by invitation): I do not think I have ever seen true eczema with such nodules. In any case of long-continued pruriginous dermatosis with nodules of this character it seems to me that one should consider mycosis fungoides. The other possibility is chronic eczema developing into lymphoblastoma—in which case the nodules would be lymphoblastomatous.

Dr. William H. Goeckerman: I should call this case one of disseminated neurodermatitis, or—as it would probably have been called formerly—chronic lichenified eczema. That chronic eczema eventuates in lymphoblastoma occasionally was excellently illustrated by Dr. Wile's lecture yesterday at the meeting of the California Medical Association, and it would seem that this case is one of that evolution. My interest in cases like this lies largely today in the cause of the disseminated neurodermatitis. Many observers still feel that in all cases the manifestations must be allergic. To this I do not agree. There are multiple etiologic factors, the principal ones of which are nervous, allergic and nutritional. My own experience has taught me that in at least some cases the condition is due to a deficiency in feeding. Just what this deficiency is I do not know as yet. However, careful study of the history will usually lead one to suspect it. This does not mean that the condition necessarily occurs in poverty-stricken families. It often suggests moderately severe prurigo. My opinion has been corroborated by the ophthalmologists' study of cataracts associated with this dermatitis in a certain percentage of cases. Some ophthalmologists feel that these cataracts point to deficiency disease. If the condition is looked on as having multiple causes, the problem will be much clarified and the clinical management improved.

Dr. Samuel Ayres Jr.: The sponsor of that term disseminated neurodermatitis has discredited it. The condition is allergic dermatitis now.

Hodgkin's Disease. Presented by Dr. Thomas W. Nisbet.

J. C., a white American girl aged 23, states that a gland in the left axilla enlarged in January 1937. This was removed at St. Luke's Hospital in San Francisco, and a diagnosis of Hodgkin's disease was made by the pathologist. From that date until August 1937 general glandular enlargement occurred. By the latter date she suffered from intense itching, night sweats, loss of weight and fever in the afternoon. About two months ago the patient noticed a brownish discoloration of the skin. This has gradually spread over the entire body. About the same time an intense thirst developed; this is not relieved by the taking of large quantities of water. From Aug. 10, 1937, until the present time she has been receiving high voltage roentgen therapy, with great improvement.

Chemical analysis of the blood on April 22, 1938, showed 26.1 mg. of nonprotein nitrogen, 3.7 mg. of uric acid, 80 mg. of sugar and 528 mg. of chlorides per hundred

cubic centimeters. The urine was reported normal. The blood count showed 2,860,000 erythrocytes and 13,100 leukocytes, with 84 per cent neutrophils, 8 per cent monocytes and 8 per cent lymphocytes. Histologic examination showed melanic pigment but no evidence of iron pigment.

DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: Because of the marked loss of weight, asthenia and pigmentation, I think there is a possibility of Addison's disease.

NOTE.—The patient died June 22, 1938. An autopsy was performed by Dr. A. G. Foord, pathologist of the Collis P. and Howard Huntington Memorial Hospital. The diagnosis was Hodgkin's disease and involved particularly the periaortic, iliac, peripancreatic and biliary lymph nodes and two left supraclavicular and one mediastinal node. The following quotation is from Dr. Foord's report: "The pigment in the skin is apparently melanin. At least it does not contain iron. There is no destruction of the adrenal glands, suggested clinically. I do not know why the pigmentation occurred. I shall endeavor to read up on the subject to find if any cases of similar involvement have been reported. The pigment in the skin is certainly not that of hemachromatosis."

Pyoderma Gangraenosum. Presented by DR. C. R. ANDERSON and DR. C. R. HALLORAN.

T. K., a woman aged 21, states that four years ago she had what was said to be acne vulgaris. Two years ago pustules began to develop and rapidly became gangrenous, and she became so weakened that she had to stop school. When she was first seen there were numerous discharging sinuses about the neck and the vulval and the perianal area. There were considerable ulceration and sloughing. The borders of the ulcers presented a somewhat serpiginous arrangement. New pustules and sinuses have been observed to develop rapidly into open ulcers. The liver and spleen are considerably enlarged. One unusual point in this case is the absence of pathologic changes in the colon.

Of the numerous forms of treatment given, including arsphenamine and sulfanilamide medication and blood transfusion, none have proved of value.

DISCUSSION

DR. WILLIAM H. GOECKERMAN: The first time I saw this patient, some months ago, I did not feel that I could fit the lesions into the picture of pyoderma gangraenosum. Today I can agree with the diagnosis. When Drs. L. A. Brunsting and P. A. O'Leary and I searched the literature at the time of our report (ARCH. DERMAT. & SYPH. **22**:655 [Oct.] 1930), it became evident that this dermatosis has been given different names and usually appears when hygienic conditions are poor. There was, for instance, a report of a severe epidemic among soldiers afflicted with dysentery during the Civil War. In our own reported series dysentery was associated with the cutaneous lesions. I recall 1 case, however, in which there was long-standing empyema. We chose the name pyoderma gangraenosum because it seemed to fit the lesions and their behavior best.

DR. KATHERINE MACEACHERN (by invitation): I believe that the enlargement of the liver and spleen is due to amyloidosis. The patient has had this chronic sepsis for over two years. Congo red has not been used, because at the time amyloidosis was considered it happened that a death resulted from intravenous use of congo red in the hospital, and the test was not being used.

The only real clinical improvement has followed administration of sulfanilamide. However, after several weeks of its use there was a marked depression of the red and white cell count. Cessation of the medication and small transfusions brought the count up. On two subsequent attempts to use the drug there was an immediate drop. The dose was started at 80 grains (5.2 Gm.) a day; this was subsequently reduced to 60 and then to 40 grains (3.9 and 2.6 Gm.).

Xanthoma Diabeticorum. Presented by DR. IRVING R. BANCROFT.

J. R., a Negro aged 43, states that about ten years ago his weight rapidly increased from 170 to 225 pounds (77 to 101 Kg.). During this time polydipsia and polyuria developed. The first cutaneous lesions appeared on the knuckles in 1931. Since then he has had evanescent lesions over the center of the body, except for pigmented areas remaining from old lesions. Since March 1937 there has been no regression of the old lesions, and new spots have appeared. Now he presents numerous single and confluent xanthomatous papules over the entire body except the face. The eyelids are free. The lesions are more numerous over the joints. Over some of the knuckles the papules are joined to form tuberose lesions the size of olives.

Laboratory tests showed: in the blood, 163 mg. of sugar, 500 mg. of cholesterol, and 8,038 mg. of total lipoid (plasma) per hundred cubic centimeters; in the urine, a trace of sugar, 4 per cent albumin by volume and 3.2 mg. of phosphorus per hundred cubic centimeters.

DISCUSSION

DR. MERLIN TREVOR-ROPER MAYNARD, San Jose, Calif.: I have observed 1 case of extensive xanthoma diabeticorum. The man was a laborer at a sugar factory. Has any one had any experience with this type of industrial contact? The man inhaled large amounts of sucrose. I wonder just what the sugar does to a patient who is not truly diabetic.

MANHATTAN DERMATOLOGIC SOCIETY

ANDREW J. GILMOUR, M.D., *President*

May 10, 1938

ANTHONY C. CIPOLLARO, M.D., *Secretary*

A Case for Diagnosis (Rosacea-Like Tuberculid of Lewandowsky?). Presented by DR. ANTHONY C. CIPOLLARO.

H. R., a man aged 40, was first seen on April 28, 1938, because of an eruption involving the face. He states that the eruption began on the forehead about a year ago and has persisted in spite of different types of treatment during the past year. He has been treated with mercury and sulfur ointments, lotions, roentgen rays and various diets. He has had a complete gastrointestinal check-up. Nothing seems to do him any good. There is no history of tuberculosis in the family or of contact with tuberculous subjects. Microscopic examination showed a long-standing inflammatory process. There was no evidence of rosacea-like tuberculid of Lewandowsky. He gave a marked reaction to old tuberculin with a dilution of 1 : 10,000,000.

The patient presents lesions on the entire face, including the forehead, the preauricular and postauricular areas, the ears and the scalp. The lesions are particularly abundant around the flush centers of the face. They are discrete pustules with an areola of erythema around each. Some appear to be inflamed papules. Diascopic pressure of some of these lesions does not show typical apple jelly nodules. The papules do not show marked infiltration. The rest of the skin is free of lesions. General physical examination by an internist revealed nothing of importance.

DISCUSSION

DR. LUDWIG OULMANN: My diagnosis is sycosis. The lesions on the face and forehead are pustular. I cannot see any rosacea or any similarity to Lewandowsky's tuberculid.

DR. ISADORE ROSEN: This patient presents two types of lesions, one which would easily fit in with rosacea and the other with a staphylococcic infection of the skin, often associated with acne varioliformis. There are numerous scars, some pustules and crusted lesions. I should therefore entertain the diagnosis of rosacea complicated by acne varioliformis.

DR. DAVID BLOOM: Has chlorhydroxyquinoline ointment been used in this case? To me the eruption appears to be a staphylococcic infection involving the hairy and glabrous skin.

DR. MAURICE COSTELLO: The eruption impresses me as papulonecrotic tuberculid. Was there an exacerbation of the eruption at the time the tuberculin test was made? It is my impression that the tuberculin test causes a transitory flare-up of this type of eruption, which is followed by temporary improvement.

DR. ANTHONY C. CIPOLLARO: I am seeing this patient for a second time. His eruption is better now than it was when I first saw him. I am not certain as to whether the improvement is due to the injection of tuberculin.

DR. GEORGE C. ANDREWS: I suggest that another biopsy specimen be taken, and if it shows a tuberculoid structure, the patient should be treated with sodium gold thiosulfate.

DR. MIHRAN B. PAROUNAGIAN: I suggest using a 5 per cent ammoniated mercury ointment, in the hope that it will benefit this condition as it does acne necrotica.

DR. ANTHONY C. CIPOLLARO: It does not seem to me that the eruption is simple folliculitis. I do not know in just what category to put it. I thought it might be rosacea-like tuberculid of Lewandowsky, even though there are clinical features of folliculitis. Practically all the topical remedies have been tried. I suggest that he be treated with small doses of sodium gold thiosulfate and if that is a failure, that injections of tuberculin be tried.

A Case for Diagnosis (Recurrent Lichenoid Dermatitis?). Presented by DR. E. WILLIAM ABRAMOWITZ.

Leo S., a Russian-American Jew aged 44, a machinist, has been presented several times with a diagnosis of possible neurodermatitis or early mycosis fungoides (ARCH. DERMAT. & SYPH. **13**:455 [March]; 725 [May]; 839 [June] 1926). It is possible that the condition of his skin started as scabies for which he used many irritating remedies, or it may have been a sequel to being gassed during the World War. There is no allergic history.

The first attack in 1926 lasted over three years and finally responded to roentgen irradiation and injection of solarson. The eruption recurred four years later (in 1930), when it consisted of lesions similar to those in the first outbreak. There was a sudden onset of itching, with the development of fine papular patches, which at times appeared moist, and later lichenoid. Solarson and roentgen therapy proved ineffective this time, and so did innumerable other forms of treatment. Finally, after one year, he was given rapidly ascending daily doses (up to 60 minims [3.7 cc.] of the 2 per cent solution) of sodium arsenate hypodermically. The treatment was continued although general symptoms of arsenical intoxication developed, because considerable improvement in the cutaneous lesions appeared. The dose of sodium arsenate was then gradually reduced, and symptoms of arsenicalism, together with all signs and symptoms of the eruption disappeared.

The patient remained well for about six years, until the spring of 1937, and then the eruption returned. No time was wasted. He was again given sodium arsenate, and in six weeks the attack was over. He only had to take up to 25 minims (1.54 cc.).

The fourth and present outbreak appeared about the same time this year (April 1938) and cleared in four weeks, also during administration of sodium arsenate, but the maximum dose was 15 minims (0.92 cc.).

General physical examination and various laboratory tests showed no abnormality. His blood counts were essentially normal except for a high eosinophil count (up to 20 per cent). Histologic examinations at times showed signs of early mycosis fungoides.

No systematic patch or food tests have been performed. Elimination of certain foods was of no avail. The cause of the cutaneous disease is unknown. It is evidently not arsenic.

DISCUSSION

DR. DAVID BLOOM: I never saw dermatitis due to ingestion of pentavalent arsenic, although I have seen keratosis and hyperpigmentation in a number of cases. I wish to ask Dr. Abramowitz if he has ever seen dermatitis caused by pentavalent arsenic.

DR. GEORGE M. LEWIS: It is interesting that arsenic has been considered by some to be a frequent cause of eczema.

DR. E. WILLIAM ABRAMOWITZ: In answer to Dr. Bloom, cutaneous reactions, including exfoliative dermatitis, to inorganic arsenic were noted in the English epidemic (Reynolds, E. S.: An Account of the Epidemic Outbreak of Arsenical Poisoning Occurring to Beer-Drinkers in the North of England and Midland Counties, *Lancet* **1**:166 [Feb. 19] 1901). Cases of arsenical dermatitis from inorganic arsenic as well as from organic preparations have been reported. I do not think that dermatologists rely on arsenic as much as formerly, probably because of the knowledge that arsenic is responsible for a number of dermatoses.

A Case for Diagnosis (Mycosis Fungoides?). Presented by DR. ANTHONY C. CIPOLLARO.

M. B., a man aged 46, was first seen on March 28, 1938, at which time he had a generalized eruption of four months' duration. The condition began first on the arms and in spite of treatment has spread over the entire body. He has been treated with injections of sodium thiosulfate, a preparation of sterile milk, various local remedies for eczema and diets of various types. He was hospitalized for two weeks, during which time he received fever therapy (typhoid vaccine). This type of treatment did not appear to improve the condition. He was then treated with unfiltered roentgen rays, receiving ⅛ erythema dose (37 r) twice a week. He began improving immediately after roentgen therapy was begun.

The patient presents lesions varying in size from that of a pinhead to that of a palm on various parts of his body. They extend from his scalp to his soles. They are slightly scaly, infiltrated, raised, oval or round, dark brown to purplish and pruritic. Some of the lesions on the side of the neck and on the buttocks are exudative.

A blood count, chemical analysis of the blood and urinalysis showed no abnormality. Histologic examination showed chronic eczema, with no evidence of mycosis fungoides. The sections were stained only with eosin and hematoxylin.

DISCUSSION

DR. E. WILLIAM ABRAMOWITZ: I suggest that a determination of arsenic be made; unless a large amount of arsenic is found in the urine and blood, I think the condition may respond to arsenical therapy.

DR. ISADORE ROSEN: This condition belongs in that group of cutaneous diseases recently described which suggest at various stages differential clinical diagnoses ranging from acute allergic dermatitis to mycosis fungoides. It is now in the stage resembling mycosis fungoides. Histologic examination during any stage is consistently reported as showing chronic dermatitis.

DR. LUDWIG OULMANN: I saw a patient with exfoliative dermatitis about twenty years ago. I called Dr. Fox for consultation. Later Dr. Rosen saw the patient at the Mount Sinai Hospital; suppurating glands were present at that

time. The condition cleared during treatment at Unna's clinic, but there was a relapse a week after dismissal. Later the patient was hospitalized twice at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital. This type of allergic dermatitis with constitutional disturbances can go on for years.

DR. MAURICE COSTELLO: The condition described by Dr. Rosen has, in my experience, been refractory to roentgen therapy. Dr. Cipollaro stated that in the case under discussion the condition responded to subfractional doses of roentgen rays, which might help to substantiate the diagnosis of mycosis fungoides.

DR. DAVID L. SATENSTEIN: I have run across a number of cases in which the clinical diagnosis was mycosis fungoides and the histologic picture showed no evidence of the disease. I am convinced that the fault lies with the laboratory technician and not with the clinician. Only standard stains have been used, and no differential stains, which are necessary. I think it is rather risky to make a diagnosis on the basis of the patient's response to roentgen rays. Because the condition cleared under roentgen irradiation does not mean that it was mycosis fungoides.

DR. ANTHONY C. CIPOLLARO: The lesions in this case resemble those exhibited in the group described by Dr. Rosen, which seem to respond after improvement of the neurogenic background. The condition is really generalized neurodermatitis. This patient's condition does not impress me as belonging to that group, because conditions of that group are cured soon after hospitalization, with little treatment. Last month I presented a case of mycosis fungoides, but microscopic examination showed dermatitis. In the case I presented tonight there were some clinical features of mycosis fungoides, but the histologic changes were those of dermatitis. Because of the response of the lesions to roentgen therapy, the marked itching, the presence of infiltrated plaques of different sizes, shapes and degrees of infiltration and the patient's failure to improve while hospitalized, I think this condition may be mycosis fungoides.

Urticaria (Heat). Presented by DR. GEORGE M. LEWIS.

B. C., a shipping clerk aged 19, states that for the past four months he has noticed itching, redness and swelling of the skin when external heat was present in his immediate environment. The holding of a hot cup resulted in the appearance of lesions on the hand. Exposure to the rays of the sun produced elevated pruritic lesions on the legs. An application of hot water in a test tube to his skin for one minute produced an elevated wheal with surrounding erythema at the site of contact. This wheal reached its maximum size in about three minutes and was still present after twenty minutes. A similar test with ice gave a negative reaction.

DISCUSSION

DR. DAVID L. SATENSTEIN: I saw a patient at the last meeting of the Brooklyn Dermatological Society, presented by Dr. Walzer, who did not respond to heat, but if ice was applied for six seconds, an urticarial lesion remained for over an hour. This occurred not only from ice but from cold water. The patient went to the seashore on a cold day and had to be taken out of the water because of a cold shock, so that while this condition is an apparently simple thing, it might have serious results.

DR. GEORGE C. ANDREWS: I think physical allergy calls for a study of hepatic function. Coproporphyrin may be found in the urine and may be a factor in the disease. For this particular patient I suggest that the potassium-diet treatment suggested by H. A. Rusk and B. D. Kenamore (*Ann. Int. Med.* **11**:1838 [April] 1938) be tried.

DR. E. WILLIAM ABRAMOWITZ: Some allergists do not accept all such cases as instances of a specific immunologic phenomenon. The patient may be made to tolerate heat by exposure to slowly increasing temperature.

DR. GEORGE M. LEWIS: This condition is an example of local urticarial hypersensitiveness to heat. There is no reaction to the application of ice and no reaction to heat applied at a remote part of the body. I considered it important to warn this patient not to drink hot fluids.

Recurrent Symmetric Herpes Simplex. Presented by DR. MAURICE COSTELLO.

T. S., a man aged 30, a barber, was first seen on May 6, 1938, in the outpatient department of Bellevue Hospital. He has herpes simplex consisting of a group of tense vesicles on an erythematous base on the dorsomedial surface of the first phalanx of the right index finger. The duration of the present attack is five days. He states that the eruption usually involves the dorsal surface of the first and third phalanx of both second and third fingers, and that it has occurred every May and October for the past fifteen years. He was treated with cowpox vaccine. He is under active syphilitic treatment.

This case of herpes simplex is presented because of the unusual regular seasonal occurrence for fifteen years and the symmetric location on the fingers of both hands.

DISCUSSION

DR. DAVID L. SATENSTEIN: I have seen a number of high school girls presenting various types of herpes, sometimes marked, in the spring and fall. These patients are given smallpox vaccination; results are obtained only in cases in which there is a positive reaction.

DR. E. WILLIAM ABRAMOWITZ: I saw a report recently of the apparent effectiveness of inoculations or injections from a herpetic vesicle in both herpes simplex and herpes zoster.

DR. MAURICE COSTELLO: It is my impression from the cases of recurrent herpes simplex in which I have used cowpox vaccine that the attack is occasionally aborted and not infrequently shortened. The interval between attacks is lengthened.

Lupus Erythematosus. Presented by DR. J. FRANK FRASER.

R. H., a woman aged 25, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital with an eruption that had been present since July 1937. It first developed on the right forearm and two months later on the forehead.

For the past two weeks the patient has been using hydrogen peroxide to bleach the skin of the forehead. The hair was accidentally bleached when the hydrogen peroxide was applied to the forehead. The patient uses phenolphthalein on rare occasions.

The lesion on the forehead is brownish, erythematous, slightly scaly and of a reticulated appearance. Brownish scaly round lesions are present on the right forearm. The patient uses a cleansing cream, which may have been an added factor.

DISCUSSION

DR. GEORGE M. LEWIS: There are violaceous flat-topped umbilicated papules on the forearms, and in some places the lesions are in streaks. I therefore suggest a diagnosis of lichen planus.

DR. DAVID L. SATENSTEIN: I think the lesion on the forehead is an example of Riehl's toxic melanosis.

DR. DAVID BLOOM: One does not see in this case any characteristics of lupus erythematosus. The reticulated pigmentation on the forehead, which may be due to exposure to ultraviolet rays, does not justify any diagnosis except hyperpigmentation.

DR. MIHRAN B. PAROUNAGIAN: I favor Dr. Lewis' diagnosis of lichen planus in this case.

A Case for Diagnosis (Bromoderma?). Presented by DR. E. WILLIAM ABRAMOWITZ.

B. K., a man aged 34, was presented before the Manhattan Dermatologic Society on April 12, 1938 (ARCH. DERMAT. & SYPH. **38**:661 [Oct] 1938), with a diagnosis of possible tinea barbae. Since then, as no fungi have been demonstrated on microscopic examination or culture, the diagnosis of tinea barbae has been eliminated. Two histologic examinations revealed an infiltration of polymorphonuclear leukocytes around the vessels of the upper and the middle part of the cutis, conforming with pyoderma. There were no signs of lupus erythematosus.

The patient showed rapid improvement under treatment with boric acid compresses and large doses of sulfanilamide. This treatment was kept up for about six days and then, owing to nausea and vomiting, the sulfanilamide had to be discontinued.

A twenty-four hour specimen of urine was examined for bromides and iodides, and the report showed 2.2 mg. of bromides per hundred cubic centimeters (a total of 27.5 mg. for the entire day). There is no history of ingestion of any medicament or other substance containing this element. The patient is now taking sodium chloride by mouth. Bacterial culture from a lesion showed nonhemolytic Staphylococcus albus. Bacteriophage has been prepared and will be used if needed.

DISCUSSION

DR. DAVID L. SATENSTEIN: All that appeared on microscopic examination was pyoderma. There were various-sized miliary abscesses in the deep tissue, with an inflammatory reaction. No granulation tissue such as one would expect in iododerma or bromoderma was present. Lupus erythematosus could be excluded. I suggested the possibility of a deep fungous infection. I do not think the condition is bromoderma.

DR. DAVID BLOOM: As far as I know, sulfanilamide is not effective in staphylococcic infection.

DR. GEORGE C. ANDREWS: I have had cases of chronic pyoderma and refractory sycosis vulgaris in which great improvement followed the use of sulfanilamide, and there is still something to learn on that score. I think that it will eventually be found that sulfanilamide is useful in some types of staphylococcic infection.

DR. GEORGE M. LEWIS: I have used sulfanilamide in an ointment in 1 case of pyoderma, and improvement resulted. In about one third of a series of cases of tinea pedis there was improvement, but I am not sure that there was any specific effect.

DR. ISADORE ROSEN: I had the opportunity to study this patient carefully on numerous occasions, and I am still in doubt as to the diagnosis. The two possibilities I entertained were (1) drug eruption (bromide or iodide) and (2) bullous lupus erythematosus.

DR. E. WILLIAM ABRAMOWITZ: If the condition is bromoderma, the patient should get well during administration of salt by mouth or by injection. As there is no history of bromide medication, he may have got the eruption in some other way (bread?). I cannot say definitely that sulfanilamide helped him, because under boric acid compresses he seemed to improve just as much. The erythematous nodular lesions point toward some drug. The patient states that the eruption became worse with each injection of a bismuth preparation.

Pachyonychia Congenita. Presented by DR. HOWARD FOX.

P. B., a white girl aged 9 years, of Irish-American parentage, first had abnormal changes in her nails at the age of 6 months. Her father and mother are living and well. She is next to the oldest of 10 children (6 brothers and 3 sisters), all of whom are living and well. No one else in her family has ever suffered from a similar disease.

The patient was a full term breast-fed infant. At 6 months of age, coincident with changes in the nails, "warts" developed all over her body, except on the face. The mother states that these warts would fall off and a blister would develop on the base. The blisters would last a week or ten days and then disappear. She does not recall when the lesions of the mouth first appeared.

The patient presents four types of lesions, including hypertrophy of the nails, various forms of verrucae, bullous lesions and leukokeratosis of the mouth.

All finger nails and toe nails are affected and present in general the same appearance, the finger nails being somewhat thicker and longer than the toe nails. All nails show great hypertrophy and grow upward at an angle of approximately 45 degrees. Most of them tend to curve forward, and a few (especially toe nails) have a lateral curve, suggesting onychogryphosis. All nails are rectangular and somewhat laterally compressed. Their length varies from ½ to 1 inch (1.3 to 2.5 cm.). There is no paronychia. The color is brownish black.

There is a generalized, symmetric and fairly profuse eruption of various types of verrucous lesions, most numerous on the lateral aspect of the trunk and the extensor aspect of the extremities. One type, most profuse on the shins and about the elbows, consists of discrete lesions the size of a small pinhead, which are aggregated in patches and feel like a nutmeg grater. A second type consists of millet-sized round warts. A third type consists of numerous filiform warts on both the trunk and the extremities from ⅛ to 3/16 inch (0.3 to 0.5 cm.) long.

On the bearing surface of the feet, and to a less extent on the lateral and dorsal aspects of the left side of the neck and the intergluteal cleft, are reddish glazed tender areas covered by sheetlike tough adherent crusts. When first observed, these lesions suggested psoriasis. The scales, however, were not micaceous, and the under surface tended to be moist. No bullae have been observed, but the patient states that "big blisters" have invariably preceded the formation of the aforementioned lesions. On the left side of the neck there is a semicircular band about 3 inches (7.6 cm.) long and from ¼ to ⅓ inch (0.6 to 0.8 cm.) wide, and of a composition like that of the lesions on the feet.

The tongue and the cheek pouches show a profuse eruption of macerated, grayish white keratotic lesions. There is a solid nickel-sized patch immediately in front of the circumvallate papillae, and bands are present along the lateral borders of the tongue. The anterior half of the dorsum presents a stippled appearance due to numerous pinhead-size whitish spots. In the cheek pouches, opposite the interdental cleft, are elevated jagged irregular masses and flat patches. None of the lesions in the mouth are painful or tender in the slightest degree.

The patient is small for her age, weighs 45 pounds (20.4 Kg.) and looks rather delicate. There are no anomalies of teeth or hair. She has a full set of teeth, some of which are carious. The hair of the scalp is brown, straight and of fine texture. She is mentally normal.

The Wassermann reaction was negative. The urinalysis showed nothing abnormal, and the basal metabolic rate was +15 per cent. A differential blood count was normal.

DISCUSSION

DR. GEORGE C. ANDREWS: I think this condition is outstanding, typical and unusual to see. The changes, such as leukokeratosis, onychosis and keratotic lesions, as Dr. Fox pointed out, and especially the location of the lesions—over the elbows—are classic. I believe the lesions on the feet are bullae. They commonly occur in this condition, and these lesions look like dried-up bullae. I think this case is remarkable. One thing to be noted definitely is the poor nutrition due to soreness of the lips and mouth. The diet should be carefully outlined.

DR. GEORGE M. LEWIS: The perlèche, the beefy tongue, the poorly nourished condition and the crusted lesions on the feet suggest the possibility of an infection due to Monilia albicans. Could this be a complication?

Psoriasis Associated with Arthritis Deformans. Presented by DR. HOWARD FOX.

C. F., a woman aged 26, a stenographer, is presented from the dermatologic wards of Bellevue Hospital. No other member of her family ever suffered from either psoriasis or arthritis. She has had an eruption for the past nine years and arthritic changes for the past six years. She presents a generalized, rather sparse eruption of typical patches of nummular psoriasis affecting the scalp, forehead, ears, elbows and trunk. The finger nails show pitting and the toe nails both pitting and subungual hyperkeratosis.

The joints of all the fingers are swollen and tender. Several are ankylosed and deformed. The joints of the toes are only slightly involved. Both shoulders show slight limitation of motion. The Wassermann reaction was negative, and the urine showed nothing abnormal. A differential blood count was within normal limits. A roentgenogram of the fingers showed atrophic arthritis involving the interphalangeal joints and wrists. No pathologic changes were noted in roentgenograms of the shoulders and sacroiliac joints. There was no objective evidence or history of gonorrhea, and the complement fixation test for this disease gave a negative result. The patient is well nourished and has a normal temperature.

DISCUSSION

DR. DAVID L. SATENSTEIN: I think that a large proportion of persons with psoriasis have arthropathy of some form or other.

DR. E. WILLIAM ABRAMOWITZ: In 2 cases, 1 of psoriasis of the nails and the other of extensive generalized psoriasis of the body, I administered large doses of vitamin D. There was no effect.

Erythema Elevatum Diutinum. Presented by DR. DAVID BLOOM.

J. H., a man aged 64, was previously presented before this society in January 1938 (ARCH. DERMAT. & SYPH. **37**:918 [May] 1938), with a diagnosis of possible lymphoblastoma or xanthoma; before the New York Dermatological Society in January 1938 (ibid. **38**:103 [July] 1938), with a diagnosis of possible mycosis fungoides or lymphoblastoma; before the Bronx Dermatological Society in February 1938 (ibid. **38**:124 [July] 1938), with a diagnosis of possible mycosis fungoides, and before the Section of Dermatology and Syphilis of the New York Academy of Medicine in March 1938 (ibid. **38**:472 [Sept.] 1938), with a diagnosis of possible Kaposi's sarcoma. As the lesions consisting of tumors and plaques have flattened, leaving pigmentation, and the lesions on the neck have entirely disappeared after ingestion of small amounts of solution of potassium arsenite during two weeks, these diagnoses have been reconsidered.

Dr. Fred Weidman has examined the slides and has definitely eliminated the diagnoses of Kaposi's sarcoma and mycosis fungoides. In the section from the knee he called attention to the relation of the subacute inflammatory process to the blood vessels, hyperplasia of the vessels with extreme toxic necrosis of their walls and hyperplasia of the fibrillae, which were more or less granular and degenerated and took the eosin stain much more strongly than normal. Some of the vessels had an almost or entirely occluded lumen but no thromboses.

The nuclei within the walls were pyknotic, and occasionally polymorphonuclear leukocytes were seen within them. These changes occurred not only within the walls of the vessels but to a considerable degree in the adjoining tissue. In the section from the neck there were only hyperplastic blood vessels showing evidence of reactive hyperplasia in the large, sometimes gigantic, size of their lining endothelial cells. Polymorphonuclear leukocytes were extremely numerous; eosinophils were conspicuous and the stroma presented hyperplasia of its spindle cells, which at times were clustered to suggest Aschoff's bodies.

Because of this picture, Dr. Weidman suggested a general intoxication of the blood stream referable to some focal infection and the diagnosis of erythema elevatum diutinum.

Two cases of this disease were described by F. D. Weidman and J. H. Besancon (ARCH. DERMAT. & SYPH. **20**:593 [Nov.] 1929). The picture in the present case conforms clinically to their description of the entity.

In the last ten days the lesion on the extremities, which were flat previously, have become elevated. The patient presents tumors and infiltrated plaques once more, although these are not of the same size as those at the first presentation.

DISCUSSION

DR. MAURICE COSTELLO: When this patient was presented at the Wednesday afternoon conference at Bellevue Hospital and later before this society, I suggested the diagnosis of erythema elevatum diutinum because of the appearance, location, distribution and behavior of the lesions.

DR. LUDWIG OULMANN: According to J. Jadassohn's handbook (Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927), the term erythema elevatum diutinum has entirely disappeared, and the eruption is grouped today with granuloma annulare.

DR. GEORGE C. ANDREWS: It would be interesting to look up Weidman and Besancon's article on the subject. As I remember, the appearance and distribution of the lesions in their cases, shown by photographs in the article, were counterparts of those in this case. What is the consensus of those present: Is there or is there not an entity of erythema elevatum diutinum?

DR. DAVID BLOOM: One reads in the literature the opinion that erythema elevatum diutinum is a variety of granuloma annulare. It is conceivable that in some cases granuloma annulare may be confused clinically with erythema elevatum diutinum. The lesions in this case, however, do not remotely resemble granuloma annulare. The condition is clinically an entity which I have never seen previously, as far as I can remember. That it is extremely rare is to be concluded from the fact that of all the excellent dermatologists who have seen this patient, Dr. Costello was the only one who suggested this diagnosis.

Acute Lupus Erythematosus. Presented by DR. GEORGE M. LEWIS.

Eczema. Presented by DR. GEORGE M. LEWIS.

CHICAGO DERMATOLOGICAL SOCIETY

HAMILTON MONTGOMERY, M.D., *President*

May 18, 1938

H. RATTNER, M.D., *Secretary*

Senear-Usher Syndrome. Presented by DR. THEODORE CORNBLEET and DR. D. COHEN (by invitation).

R. P., a woman aged 21, states that in October 1936 a small "blister" appeared on the back of her neck, accompanied with intense pruritus. Scratching of apparently normal skin was followed by the appearance of new bullae. The original lesion was present for about one month before other lesions appeared on the back, chest and abdomen and finally on the face by gradual extension. The patient thinks that there was some involution of the lesions on the back but none on the face or abdomen during the entire period.

There is now a generalized eruption on the face, back, abdomen, chest and extremities. The lesions begin as bullae, which rapidly break and form a brown

crust. This lasts for about one week and then disappears, leaving a brownish pigmented ring. On the chest there are small white atrophic scars. On the nose and left cheek are erythematous plaques with a white, loosely attached scaly crust. Patches of dermatitis on the scalp, face and body mimic those of seborrheic eczema.

DISCUSSION

DR. F. E. SENEAR: I should like to hear Dr. Ormsby discuss this case. I think that in all essentials the picture closely resembles that in one of his early cases. The distribution of the eruption and the facts that it is vesicular at times and that it leads to the development of keratotic lesions makes it one of the most typical since Dr. Ormsby's original presentation. There has been much discussion as to whether the condition should be classed as relatively benign pemphigus or as lupus erythematosus; I think, as Dr. Wise brought out, that in some cases presented as instances of pemphigus the condition belongs in the lupus erythematosus group. I am open-minded on this point, but as in some the condition has developed into typical pemphigus vulgaris terminating in death, I think one must concede that in some cases it definitely belongs in the pemphigus group. The clinical picture varies so greatly that in some cases diagnosed as instances of lupus erythematosus the condition really belongs in the pemphigus group.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Dr. Ormsby once asked me to study a slide in a typical case of this syndrome. The histologic picture was not that of lupus erythematosus, nor did it present features of pemphigus. The histologic picture of lupus erythematosus is distinctive, whereas that of pemphigus may be confused with various bullous dermatoses. Many cases reported as instances of Senear-Usher syndrome have proved to be cases of either disseminate lupus erythematosus or ordinary pemphigus. I suggest that specimens be taken for biopsy in this case, both from the lesions on the abdomen and from a lesion on the face.

DR. OLIVER S. ORMSBY: After reviewing the cases I have observed, together with some recorded in the literature, I feel sure that there is a syndrome presenting symptoms of lupus erythematosus, seborrheic eczema and pemphigus in combination. On the face there is a chronic type of crusted dermatitis resembling lupus erythematosus; on the trunk and sometimes on the extremities bullae develop and later become crusted areas resembling patches of seborrheic eczema. The original case of this group was shown before this society by Dr. J. H. Mitchell and me seventeen years ago (ARCH. DERMAT. & SYPH. **4**:284 [Aug.] 1921). In the discussion that followed benign pemphigus and lupus erythematosus were suggested. Under treatment with arsenic the patient made a complete recovery; I have seen him recently, and his disease is entirely eradicated. This case, together with another of ours in which there were more active symptoms, was included in F. E. Senear and B. Usher's report on this condition. (ARCH. DERMAT. & SYPH. **13**:761 [June] 1926). The second patient has also been entirely well for several years. I have observed several other cases since that time in which the clinical picture is like that under consideration. The subject has been confused in the literature by the recording of cases which were instances either of true lupus erythematosus disseminatus or of ordinary lupus erythematosus with bullae. Typical lupus erythematosus with bullae has long been recognized.

DR. THEODORE CORNBLEET: As has been mentioned, it is difficult to differentiate this condition from disseminated lupus erythematosus on the one hand and from pemphigus on the other. One reason, I think, is that these patients are not at all toxic. Their blood is not toxic for the seedlings used in the Pels-Macht test. I found that the use of vitamin C is helpful for the toxemia in ordinary pemphigus, but I have used that same material in cases like this without any benefit. One would not expect much help from this agent, for these patients are not sick. One patient at Cook County Hospital had a rather disseminated form of the eruption. For years he did not feel ill; then gradually progressive toxemia developed, the eruption extended and he died. Dr. Wien and I thought at the end

that his condition was real pemphigus. As in some other grave syndromes, this one pursues a relatively benign course for a long time before the terminal toxemia sets in.

Lupus Erythematosus Disseminatus Subacutus. Presented by Dr. M. H. Ebert and Dr. David V. Omens (by invitation).

M. A., a white woman aged 40, presents an eruption which first appeared on the backs of the hands about three months ago. One year ago she suffered from rheumatic stiffness in the hips; during the preceding three months this had extended into the legs. Slight exertion caused fatigue. Five months ago a tumor was discovered in the right breast and was diagnosed as carcinoma. Surgical intervention was refused; roentgen therapy was administered daily from March 31 until April 25. She has lost little weight and now weighs 153 pounds (69.4 Kg.).

There is a deep purplish flush over the forehead, temples, ears, eyelids, nose and chin. Erythema with some scaling is present on the upper part of the back and chest, the extensor surfaces of the arms and the back of the hands. At the margins the eruption is follicular and punctate; some of the puncta appear hemorrhagic. There is a similar eruption on the anterior surfaces of the thighs. Some redness and edema are present in the basal nail folds. A small milky patch is present on the left buccal mucosa, and there is some scaling of the vermilion borders of the lip. A hard lemon-sized palpable mass is noted in the right breast.

Her temperature has ranged from normal to slightly above. Urinalysis showed no abnormality. The leukocyte count was 9,600; the blood pressure 100 systolic and 80 diastolic, and the basal metabolic rate +5 per cent. An electrocardiogram was interpreted as showing some myocardial degeneration. A roentgenogram of the chest showed no abnormality except increased hilar markings.

DISCUSSION

Dr. Otto H. Foerster, Milwaukee: I think the members can all accept the diagnosis. It is only in relatively recent years that this clinical condition has been observed frequently and is not considered uncommon. I think Dr. Ormsby will agree that there has been a change in the clinical manifestations that enter into the picture of the widespread types of lupus erythematosus. Dermatologists are now familiar with gradations varying from the acute fulminating fatal type with profound changes in the blood-making organs to the mild disseminated forms from which the patient often recovers. I am increasingly impressed by the changing clinical picture of dermatoses, and I think this is shown more, perhaps, in lupus erythematosus than in any of the other grave types of cutaneous disease.

Dr. Theodore Cornbleet: There are follicular hemorrhages, particularly on the hand, such as I have observed in a number of cases of disseminated lupus erythematosus. Because of the leukopenia, so common in this disease, I have attempted to use pentnucleotide, without any benefit. I have estimated the amount of vitamin C in the blood and have found it decreased, but supplying this apparent need did not help the general course of the disease. Sulfanilamide, in my experience, has not been of any help either.

Dr. Oliver S. Ormsby: I think it is extraordinary that these patients are so ill and that so little can be found to account for the desperate illness. Dr. Schmidt and I now have a patient suffering from acute lupus erythematosus disseminatus of the face and extremities; she is very sick. Her leukocytes number only 3,000, and she is running a high temperature. She had a sinal infection; drainage produced no benefit. She also has an infection of the throat, but there is nothing specific in that. Roentgenograms of the chest and blood cultures have shown no abnormality. I think one cannot always make a diagnosis from the cutaneous lesions alone, for there are a number of leions of variable types. When the picture originally described by Kaposi as erysipelas perstans faciei is present, it is possible

to place the condition from the cutaneous symptoms. In several cases Dr. Schmidt and I have made variable observations at autopsy. In 1, tuberculosis (both primary and terminal) was seen, and in another endocarditis and other cardiac changes. I think the Libman-Sacks syndrome is a form of acute lupus erythematosus disseminatus. We have used various methods of treatment, but a large percentage of the patients have died.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Dr. O'Leary and I recently saw a patient who was examined in the clinic about ten years ago because of chronic lupus erythematosus and whom we saw a year ago because of subacute disseminate lupus erythematosus. She had numerous infected teeth and septic tonsils, of which we advised removal only after the cutaneous lesions had quieted. She underwent tonsillectomy at home, and immediately an acute exacerbation developed. She returned to the clinic with acute disseminate lupus erythematosus, leukopenia, arthritis and nephritis. The patient failed rapidly and died within six weeks. J. B. Ludy and E. F. Carson (ARCH. DERMAT. & SYPH. **37**:403 [March] 1938) recently called attention to the presence of lead in the urine in this disease, and our patient was found to have large amounts of lead in the urine shortly before death. In the present case an investigation should be made for the presence of lead.

DR. M. H. EBERT: I appreciate the discussion, particularly the suggestion of Dr. Montgomery about searching for lead, which we certainly shall do. Dr. Ormsby brought out the point that this disease is truly systemic and the cutaneous manifestations only incidental. A feeling of malaise and of being tired all the time and all the symptoms of severe illness developed several months before the cutaneous lesions appeared.

A Case for Diagnosis (Schamberg's Disease?). Presented by DR. THEODORE CORNBLEET and DR. D. COHEN (by invitation).

C. L., a woman aged 33, presents a dermatosis involving the lower two thirds of each leg, of sixteen years' duration. According to the patient the onset was not gradual; when she was 17 years old the entire eruption appeared suddenly, and thereafter there was no further progression, and no additional lesions formed.

The eruption is brownish, macular and retiform, and several purpuric spots are present.

The patient has essential hypertension; the blood pressure is 240 systolic and 100 diastolic.

Histologic examination showed a thin non-nucleated scale. The epidermis was flattened and showed slight intracellular edema and a continuous basal layer. Throughout the corium there were slight infiltration about the blood vessels and many granules of brown pigment both within and outside the cells. These were shown to be hemosiderin by Perles' prussian blue test.

DISCUSSION

DR. F. E. SENEAR: I have no definite opinion about the case, but to me the condition does not appear to be Schamberg's disease. The lesions seem to be purely pigmentary, without the red color commonly seen, and the eruption seems more uniformly distributed than in Schamberg's disease. It impresses me more as a type of pigmentation following some acute purpuric exanthem.

DR. A. W. STILLIANS: Schamberg named the condition progressive pigmentary dermatosis. I see little evidence of progression in this case, but the disease may be in a quiescent period.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: The histologic picture was typical and consistent with a diagnosis of Schamberg's disease. The sections showed marked deposits of hemosiderin outlining the reticuloendothelial system and showed interchange of pigment from basal and dendritic cells in the epidermis, by way of chromatophores to the blood vessels in the upper part of the cutis.

The section did not show inflammatory changes or obliterated changes in the deeper vessels, such as one would expect if the disease were simple stasis or varicose dermatitis.

DR. M. H. EBERT: I noticed on the thighs, far from the pigmented area, little bright red points that did not fade on diascopic pressure. It seems to me that the primary change is in the blood vessels, and I think this point should be studied further.

DR. CLARK W. FINNERUD: I am surprised to find that histologically this picture is a good example of Schamberg's disease although clinically it is not.

DR. THEODORE CORNBLEET: We had difficulty in classifying this condition, but we believe the cayenne pepper spots of Schamberg's disease are present and that the general arrangement of the pigment is characteristic. The progressive element is lacking, as Dr. Stillians stated. The patient says that the entire eruption came on sixteen years ago and has not changed materially since. She has definite hypertension, but whether this was present when the dermatosis appeared sixteen years ago is impossible to say, although such a finding would be rather improbable at the age of 17. The degree of hypertension is unusual for her present age. It is possible that the hypertension may give rise to extravasations which produce the pigment. We feel that the diagnosis is not definitely settled, but are willing to accept the diagnosis of Schamberg's disease for the present.

Herpes Zoster in a Child Aged 4 Years. Presented by DR. H. RATTNER.

H. J., a Negro aged 4 years, has herpes zoster involving the left side of the trunk, of four days' duration. It was not preceded by pain, and he complains of only slight pruritus. He has not had chickenpox, nor has he been exposed to it, so far as is known.

DISCUSSION

DR. H. RATTNER: I gave this boy an injection of vitamin B_1 in the form of thionine chloride yesterday. I think he has shown improvement. I have treated about 10 patients with this preparation, with indifferent success for the most part. Where I hoped for good results, in postzoster pain, I have been disappointed.

DR. OLIVER S. ORMSBY: Several years ago the question of regional adenopathy was emphasized in this disease, and this boy shows definite adenopathy. Children usually have no pain, but generally some pruritus.

DR. CLARK W. FINNERUD: I wish to ask whether any one has any suggestions, aside from that of using vitamin B, analgesics and narcotics, for the management of postzoster pain in elderly persons. In two cases I have seen herpes simplex recurrens associated with decided lymphadenopathy (regional); in 1 it was responsible for zosteriform scarring.

DR. M. H. EBERT: In a few instances positive results of animal inoculation with material taken from patients with herpes zoster have been reported. This was later explained on the ground that the material was taken from patients with herpes simplex with regional adenopathy rather than with herpes zoster.

DR. M. E. OBERMAYER: Intravenous injections of a preparation of methenamine and sodium salicylate have sometimes given good symptomatic results, relieving pain and speeding healing in herpes zoster.

Clinical differentiation between herpes zoster and herpes simplex is often impossible, since both conditions may exhibit exactly the same symptoms and signs, including unilateral distribution, adenopathy and pain. The only certain way of differentiation is inoculation into the cornea of a rabbit of material from a lesion.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: In the early stages of postherpetic neuralgia, paravertebral roentgen therapy is often of great benefit, as has been emphaszed by Dr. H. R. Foerster (ARCH. DERMAT. & SYPH. **25**:256 [Feb.]

1932). In older patients who have herpes zoster the frequent association of malignant growth and especially of lymphoblastoma as precipitating factors of herpes zoster must be kept in mind.

DR. OTTO H. FOERSTER, Milwaukee: I have used paravertebral roentgen therapy with the technic described by Dr. H. R. Foerster in this disease for many years with satisfactory results.

Prurigo in Mother and Daughter. Presented by DR. M. E. OBERMAYER.

V. D., a woman aged 36, presents an eruption of the legs, thighs and sacrum, accompanied with intense pruritus, which has been present since she was 3 years of age.

Around both thighs and legs, especially on the extensor surfaces, is an eruption consisting of discrete match head-sized papules, many of which are excoriated. The involved surfaces show lichenification, pigmentation and scarring. There is inguinal adenopathy.

Physical examination and laboratory tests gave results essentially within normal limits. The patient was shown before this society by Dr. Ebert on Oct. 15, 1930 (ARCH. DERMAT. & SYPH. **23**:372 [Feb.] 1931).

L. D., the patient's 5 year old daughter, has a pruritic eruption of the face, neck, extremities and trunk, which followed an attack of scarlet fever three years ago. The lesions began as small erythematous wheals resembling insect bites; these were soon succeeded by dull red papules, varying in size from that of a pinhead to that of a hempseed. These in turn became excoriated. There has been some improvement during the winter.

Physical and laboratory examinations showed no abnormalities.

Biopsy sections of both patients are presented.

DISCUSSION

DR. OLIVER S. ORMSBY: Were these cases presented as instances of prurigo?

DR. HAMILTON MONTGOMERY, Rochester, Minn.: The histologic concept of transition between urticaria, lichen urticatus and prurigo of Hebra was first suggested by Civatte and later corroborated by Gans. Frequently a condition at first glance may be regarded as prurigo of Hebra and prove when studied further to result from numerous systemic or localized conditions. I do not feel that the clinical picture in Dr. Obermayer's case fits in with that of prurigo of Hebra, although the child has lichen urticatus.

DR. OLIVER S. ORMSBY: It is a little beside the point to discuss prurigo of Hebra, for the case was not presented as an instance of that disease, but it may be worth while to mention some of my experiences with this disease. It begins in infancy or while the patient is very young and lasts throughout life. After a certain time the skin becomes pigmented and thickened, and there is generalized adenopathy, due probably to secondary infection from scratching. The patients at the age of 16 usually look as if they were about 9 or 10. Due to the constant irritation, sleep is disturbed and nutrition is interfered with; the growth is stunted, and one sees a wizened child. There have been several cases of prurigo of Hebra in this country, all imported. As an urticarial complication occurs early in these cases, Colcott Fox decided to study lichen urticatus from that standpoint. He selected a large group of cases of lichen urticatus and observed them for ten years. I observed some of the cases while I was with him for a year, and in none of them did prurigo of Hebra develop. He concluded that there was no connection between the two diseases. I have observed a condition like the one seen today in a number of cases, and I feel that it hardly fits in with neurotic excoriation. In the last-named disease pruritus is not pronounced, but the patient feels as if something is in the skin that should be removed. The English term the condition "dug-out lesions." Prurigo nodularis is simulated in the present case, but the condition is not prurigo nodularis.

DR. M. H. EBERT: Dr. Obermayer was kind enough to inform me that he was about to present this case again. I had the opportunity to read over the discussion occasioned when I presented the case in 1930. The lesions have changed little. They are still confined to the lower extremities, and the excoriated papules, areas of lichenification and scars are still present. The case was presented as one of neurodermatitis, with a question mark. Many of the conditions discussed today were discussed on that occasion. Some of the members are still inclined to believe as I did then, that all the lesions present today could be produced by scratching on a neurogenic basis.

DR. OTTO H. FOERSTER, Milwaukee: This case was presented under the diagnosis of prurigo of Hebra of mild type. Prurigo of Hebra is almost unknown in this country. As Dr. Ormsby said, the cases are all recent importations. The clinical picture of the severe, or ferox, type described by Dr. Ormsby is striking, and I wish only to add that in addition to the wizened appearance there is a peculiar "dusty" appearance. Palpation reveals a definite thickening of the skin that is more than lichenification and increases characteristically from above downward. In the patient presented the thickening occurs chiefly in linear bands and involves restricted areas. There may be as few lesions as in the case presented by Dr. Obermayer, but I think that pigmentation and diffused thickening of the skin are always present, even in the mild types. I am not inclined to accept this condition as an example of mild prurigo of Hebra, even though it has been present since the patient's third year.

DR. M. E. OBERMAYER: If I still sustain my diagnosis of mild prurigo of Hebra against the suggestions made, it is partly because of my experience in Austria, where prurigo is common, and partly because actual clinical differences allow a differentiation of the disease. There is no other cutaneous entity which regularly starts so early in life and continues to be present through the years with no seasonal variations; there is no other disease in which the primary lesions year in and year out are of the same type: pruritic papules which show no tendency to coalesce; there is no other disease which keeps to its sites of predilection as obstinately. In this patient the eruption has remained localized in the areas shown today, and she never has had lesions elsewhere.

It is true that the extensive pruritus, the adenopathy and the scarring can be present in other chronic pruritic conditions of long standing. However, these features are seldom as pronounced as they are in this case. To interpret this case as one of lichen simplex chronicus would mean to take a secondary lichenification for a primary disease. Lichenification is present only in striate form, which makes the explanation that it developed secondary to scratching even more convincing.

It is true that the child has, up to now, shown only the features of lichen urticatus, but on the continent at least this condition is often the forerunner of prurigo. It will be of interest to follow the course of the disease in mother and child.

Pemphigus Treated with Mercurochrome. Presented by DR. M. H. EBERT and DR. DAVID V. OMENS (by invitation).

W. H., a German-American man aged 26, states that six months prior to being admitted to the Cook County Hospital, on Jan. 31, 1938, he had "sores" in the mouth, which were in constant evolution and were accompanied with no cutaneous lesions. Two weeks before entering the hospital he noted bullae on the skin of the extremities, which rapidly spread to the trunk and became generalized as a discrete bullous eruption. Some of the bullae contained clear serum and others a lactescent substance. Examination at the hospital showed a generalized bullous eruption, the lesions varying in size from that of a finger nail to that of a palm. There were areas of denudation, especially at points of pressure.

Treatment consisted of bathing with potassium permanganate and use of sodium perborate as a mouth wash. During the period from Feb. 8 to April 7, 1938, six blood transfusions of 500 cc. each were given. Sulfanilamide was administered for ten days, with no improvement. Intravenous administration of 1 per cent solution of mercurochrome was started on April 3 and continued until April 18, the dose being started at 3 cc. and increased to 15 cc. in the course of seven injections. On April 23 a definite improvement was noted: no new lesions appeared. Since May 3, 2 cc. of 1 per cent mercurochrome has been given intravenously daily.

DISCUSSION

DR. THEODORE CORNBLEET: The first time I saw this patient my impression was that the eruption was erythema multiforme. At that time probably the only primary lesions were bullae, but these were rather extraordinary in their arrangement, all being definitely iris-like. I could count as many as three annular bullae surrounding one another in bull's-eye fashion. The man had a great deal of pruritus and appeared toxic, but that, I think, can be explained on the basis of the extensive eruption. Later I was willing to accept the diagnosis of pemphigus, for the iris-like arrangement had apparently disappeared and in its place there was more or less extensive denudation of the skin. All the physicians observing the man felt that he would die and thought that the correct diagnosis was pemphigus vulgaris. In view of the turn of events, the diagnosis, in my opinion, is still unsettled. I am not one of that group, however, who question the diagnosis of pemphigus in a patient that recovers. In too many cases recovery has occurred after competent observers have made a diagnosis of pemphigus. However, many different agents were used in producing these various recoveries. Yet, on the other hand, none of these sporadically successful agents can be relied on for repeated success.

DR. H. RATTNER: The only thing that seemed to bring about any improvement was the treatment with mercurochrome. No apparent change followed other medication, and the patient's condition was becoming alarming.

DR. OLIVER S. ORMSBY: Concerning the use of mercurochrome in pemphigus, I have not had any success with it, but have observed the recovery of a patient with pemphigus under Dr. Omens' treatment with mercurochrome. The patient had been treated by various means without results before Dr. Omens gave mercurochrome, and he has been well for several years. In 1 case in which I used the Davis method the apparent recovery was so striking that I presented the patient at the annual meeting of the Chicago Dermatological Society (ARCH. DERMAT. & SYPH. **12**:422 [Sept.] 1925). Some months later he had a recurrence; I used the Davis treatment and later mercurochrome without beneficial result, and the disease progressed to a fatal termination.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I wish to emphasize that mercurochrome as used in the past, in large doses in the treatment of various infectious diseases, frequently resulted in severe damage to the kidneys. In regard to the use of sulfanilamide in the treatment of pemphigus, Dr. O'Leary and I have seen rather prompt involution of cutaneous lesions during this medication. The effects on the lesions of the mucous membranes have not been so striking, and a prolonged period of observation will be necessary before any definite statement can be made as to the value of this drug in the treatment of pemphigus. May I emphasize that if sulfanilamide is used in pemphigus or lupus erythematosus the patient should be kept out of the sun while receiving treatment? The use of sulfanilamide or similar compounds often renders a patient sensitive to light and may result in extensive sunburn, generalized erythema multiforme or even lesions resembling acute disseminate lupus erythematosus.

DR. M. H. EBERT: This case emphasizes again the unfortunate status of dermatology in regard to classification of these serious bullous eruptions. There

are a large number of cases at the Cook County Hospital. If the patient lives it is decided that the disease was not pemphigus, but if he dies it was. If Dr. Omens has introduced a treatment that will cure pemphigus, then it will be impossible to make a diagnosis.

DR. DAVID V. OMENS (by invitation): I became interested in the use of mercurochrome after reading an article by Dr. Hugh H. Young, of Baltimore, who was experimenting with the use of mercurochrome as a urinary antiseptic. He used the substance in a case of psoriasis and he found the disease cleared with no other treatment. Dr. Young also used this drug in the treatment of erysipelas, with good results.

I therefore began using it in the treatment of chancroidal infections, while working in Dr. Ormsby's clinic, and the results were miraculous. Later I used mercurochrome in treating a woman with pemphigus vulgaris whom Dr. Ormsby has seen in his clinic. She was 68 years of age, and the pemphigus was complicated by bronchopneumonia. The condition cleared entirely, and the patient remained free from the eruption up to about six or eight years after being discharged from the hospital. She received daily injections of a 1 per cent aqueous solution of mercurochrome, dosage being started at 5 cc. daily and rapidly increased to 20 cc. daily. The maximum dose caused gingivitis and some bloody stools, which were readily controlled.

Since then I have used the drug in 3 more cases successfully. The case presented today is the second which Dr. Ormsby has observed in which complete cure followed the used of the drug. Since pemphigus is a fatal disease, I feel that nothing is lost in experimentation with mercurochrome, and if only a small percentage of patients can be saved, the prognosis is considerably better than that accepted in the past.

Leukemic Reticuloendotheliosis. Presented by DR. F. T. BECKER, Duluth, Minn. (by invitation).

Mrs. O. M., aged 49, first noticed a pruritic papular eruption in the spring of 1934. At that time no definite diagnosis could be made. Physical examination then showed an elevation of blood pressure to 170 systolic and 90 diastolic. Renal glycosuria was present; this was controlled by diet. At this time the white blood count was 6,000, with a differential count of 55 per cent polymorphonuclear leucocytes, 14 per cent large lymphocytes, 18 per cent small lymphocytes, 3 per cent monocytes, 6 per cent eosinophils and 4 per cent immature lymphocytes. The dermatitis persisted without much change. In November 1935 her gallbladder was removed; during convalescence thrombophlebitis developed. The cutaneous eruption became progressively worse and nearly generalized. Just prior to menstruation her skin would become erythematous, much more edematous and pruritic. At the end of twenty-four hours the skin would exfoliate in large sheets. This would continue for three or four days, after which the swelling would subside, leaving orange-red patches of dermatitis, nearly generalized. Because of the apparent relation to menstruation, a castration dose of deep roentgen therapy was given in the spring of 1937. There was slight improvement for several months, but the periods of exacerbation have returned once or twice a month, usually about the first and the fifteenth.

My first examination, in December 1937, revealed large patches of slightly scaly orange-red dermatitis involving the face, neck, trunk and extremities. There was generalized lymphadenopathy. The spleen could not be palpated.

Histologic examination of the skin by Dr. E. T. Bell, of Minneapolis, and Dr. G. L. Berdez, of Duluth, Minn., showed a leukemid reaction of the erythroderma type; a cervical lymph node showed hyperplasia. Biopsy of bone marrow showed nothing abnormal. Studies of the blood at this time revealed a white count of 14,000, 96 per cent hemoglobin and a differential count of 23 per cent polymorphonuclears, 9 per cent myeloblasts, 18 per cent large lymphocytes, 45

per cent immature lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. The red blood cell count was normal.

Irradiation of the regional lymph nodes, the spleen and the skin has resulted in little improvement. Smears of blood have been studied by Drs. W. D. Coventry and Hal Downey, who have separately reached the same conclusions: (1) that they have never seen blood like this; (2) that many of the lymphocytes are immature, but the immaturity is not like that seen in ordinary lymphatic leukemia, but suggests origin from the reticuloendothelial system, and (3) that this blood shows leukemic reticuloendotheliosis in which differentiation is along lymphatic lines.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Accepting Dr. Downey's diagnosis of leukemic reticuloendotheliosis, I think the picture in this case fits in well with that in a series of 4 cases of exfoliative dermatitis associated with monocytic leukemia of Schilling which I have reported with C. H. Watkins (*Proc. Staff Meet., Mayo Clin.* **13**:294 [May 11] 1938).

DR. M. E. OBERMAYER: Examination of the blood today by the department of hematology showed a differential count of 25 per cent polymorphonuclears and 75 per cent small lymphocytes; there were no immature cells. The blood count showed 14.6 Gm. of hemoglobin (by the method of Newcomer), 4,120,000 red blood cells and 9,500 white blood cells. No unusual cells could be seen; the diagnosis was simply chronic lymphatic leukemia. This change from the previous picture may well be due to roentgen therapy.

Actinomycosis. Presented by DR. OLIVER S. ORMSBY and DR. W. W. TOBIN (by invitation).

Ehlers-Danlos Syndrome. Presented by DR. MARCUS R. CARO and DR. H. RATTNER.

Fixed Eruption, Circinate and Bullous. Presented by DR. M. H. EBERT.

PHILADELPHIA DERMATOLOGICAL SOCIETY

FRANK C. KNOWLES, M.D., *Chairman*

May 20, 1938

THOMAS BUTTERWORTH, M.D., *Secretary*

A Case for Diagnosis (Purpura Annularis Telangiectodes?). Presented by DR. SIGMUND S. GREENBAUM.

M. C., a white woman aged 42, states that five years ago small red puncta developed on the ankles and increased in size to about 1 cm. At that time she also noticed a brownish discoloration of the legs extending from the knees down and small ulcers on her feet. She was treated by a private physician, and the ulcers healed. Pigmentation and telangiectasia remained. Two years later ulcers reappeared and were healed by the same physician. The present attack is her third. Four weeks ago the patient noticed swelling and redness on the right internal malleolus. The condition spread, and ulcers appeared. The skin of the lower extremities is smooth, shiny, thin and somewhat livid. There are brownish ill defined areas of pigmentation on the lower third of each lower extremity. Telangiectasia is prominent, and there are frequent purpuric papules over the

dorsa of the feet and around the ankles. There are atrophic areas and scars resulting from old ulcerations and small ulcerations on the left sole and on the right malleolus. Urinalysis showed no abnormality, and the Kahn test was negative. The basal metabolic rate is —3 per cent; the blood count was within normal limits, and a fragility test showed beginning hemolysis in 0.44 per cent sodium chloride and complete hemolysis in 0.26 per cent. Chemical analysis of the blood showed 87 mg. of sugar, 16 mg. of urea nitrogen and 484 mg. of chlorides per hundred cubic centimeters; the carbon dioxide–combining power of the plasma was 57 cc. per hundred cubic centimeters.

DISCUSSION

DR. JOHN H. STOKES: I had a brief view of the patient and hesitate to offer a diagnosis. In most conditions like this in women I think of a tuberculous background and the possibility of erythema induratum in some of its modifications. Ulcers accompanied with little surrounding infiltration are possible in that disease sometimes, and the long duration, the tenderness and the final recovery under almost any therapy that is reasonably well directed at hygiene is a common observation. In the 3 or 4 cases of purpura annularis telangiectodes that have come under my observation there have been no ulcers. The purpuric lesions were more numerous, better defined, more abundant as a whole and not so sharply confined to an area of stasis of the legs as in this case. Those considerations make me hesitate to accept that diagnosis.

DR. SIGMUND S. GREENBAUM: I agree with Dr. Stokes concerning the ulceration. The description of Majocchi's disease does not include ulceration but does mention hemorrhagic scarring. A photograph of a patient with Majocchi's disease in O. S. Ormsby's book (A Practical Treatise on Diseases of the Skin for the Use of Students and Practitioners, ed. 5, Philadelphia, Lea & Febiger, 1937) shows several ulcerations similar to those this patient presents. The fact that she has dark pigmented or purpuric spots from which telangiectases appear to be radiating seems to indicate that the only place in which the condition could be classified is among the atypical forms of Majocchi's disease.

Lichen Amyloidosus and Prurigo Associated at One Time with Pseudopolycythemia and Visceral Suppuration. Presented by DR. SIGMUND S. GREENBAUM.

J. R., a white man aged 66, was seen in July 1928 because of an extensive extremely pruritic papular eruption distributed on the lower extremities, especially the legs, and essentially of the same character as that now present. It had been present for over ten years but was not progressing to any degree. A provisional diagnosis of lichen planus obtusus was made. Roentgen irradiation had no influence on the eruption. The patient was seen from time to time during 1929 and then not again until February 1938. He has not been ill in bed once in the past fourteen years, but has had chronic tracheitis for years. He now presents pruritic acutely developed strophulus-like lesions on the trunk. On the legs, particularly the outer surfaces, there are many lesions similar to those originally seen in 1928. These appear as hard discrete pinkish elevated papules varying in size from that of a pinpoint to that of a pinhead after the scales covering them are cleared off to expose their smooth surfaces. Itching develops only when the parts are touched. His urine was purulent in 1924, but this condition cleared after a median bar operation on the prostate. A test of the urine two days ago showed the specific gravity to be 1.01, with a distinct trace of albumin and many white cells—i. e., definite pyuria (origin unknown). The blood count was normal. Allergic tests showed the patient to be faintly susceptible to flounder, herring, lamb, liver, goat's milk, olive, orange, pea, peach, pecan, red and green pepper, salmon and shad. There was a positive reaction to a local congo red test. Histologic examination

showed amyloid infiltration in the papillary layer and hyperkeratosis. The case was previously reported by Drs. Leon Herman and B. B. V. Lyon (*Ann Surg.* **73**:223 [Feb.] 1921) as pseudopolycythemia without mention of the eruption on the skin.

DISCUSSION

DR. FRED D. WEIDMAN: The sections showed that there was no question about the diagnosis. There was a reaction in response to methylrosaniline, but for some reason or other the red color showed up well under artificial light; generally it does not. I should like to examine the remaining sections to study the condition of the arteries. In a case of generalized amyloidosis the parts around the arterial walls contain amyloid. As Dr. Greenbaum said, the patient has a large focus of suppuration, which is the best established cause for general amyloid disease.

Lichen Planus Chronicus. Presented by DR. H. J. SMITH.

M. S., a white man aged 67, presents an eruption limited to both legs, consisting of grouped flat papules which spread by coalescing to form slightly indurated purple patches with lighter colored centers, irregular borders and a fine white scale. The color does not fade under diascopic pressure. At various puncta the color is accentuated. There are fine superficial telangiectases scattered around the lower third of both thighs. In addition there is a crusted eczematous patch 8 by 10 cm. on the right calf. There is edema of both ankles. The duration of the condition is six years. It had its onset after the patient bathed in the ocean, with swelling of both ankles. The patient was confined to bed for three months with chills and fever. He received local application of iodine and magnesium sulfate. After three months there was a "dime-sized red spot on the right calf." After he applied salve the skin became exudative over this area. Four to five months later the left leg became involved. After this there was a steady slow progression, with occasional remissions, which never left the area entirely free. The heart is enlarged 3 cm. to the left of the nipple line, and the sounds are of poor quality, the first sound being roughened at the mitral area. The blood pressure is 150 systolic and 80 diastolic. There are signs of sclerosis of the peripheral vessels. The liver is enlarged 3 fingerbreadths below the right costal margin. Serologic tests of the blood were negative; two chemical analyses showed 79 and 83 mg. of sugar, 16 and 17 mg. of urea nitrogen, 3.5 and 3 mg. of uric acid and 178 mg. of cholesterol. Urinalysis and a blood count showed no abnormality. Biopsy on two occasions in the past six months showed simply chronic diffuse dermatitis. Administration of 75 r of unfiltered radiation weekly for four doses produced no results, and the treatment was discontinued. The elastic bandage was prescribed for support, as was a mild antipruritic ointment.

DISCUSSION

DR. FRED D. WEIDMAN: From the clinical side I favor Kaposi's sarcoma. I think the pseudoelephantiasis around the bases of the toes is clearcut and one of the most useful signs available for clinical diagnosis of Kaposi's sarcoma. The sections were so poorly prepared that they did not bring any message at all. I am told that they showed subacute dermatitis. I think that must be due to the selection of the lesion—probably a regressing lesion was selected and for that reason the picture of Kaposi's sarcoma did not appear. I feel sure that the case is one of Kaposi's sarcoma.

DR. JOHN H. STOKES: I should like to point out that in tuberculosis the same elephantiasis at the base of the toes that Dr. Weidman sets down as a significant point in Kaposi's sarcoma can be present. Of course, without a section I cannot discuss this case further, because there are too many possibilities, but the elephantiasis does not necessarily make the condition Kaposi's sarcoma.

DR. SIGMUND S. GREENBAUM: This man has a cardiac condition, and the liver is enlarged. It is a question how much of the swelling of the leg is pure edema and how much real elephantiasis.

DR. FRED D. WEIDMAN: The pseudoelephantiasis that I was referring to at the base of the toes has a hard woody quality. There is also, of course, the edema in the legs. In the absence of lesions such as the patient has on his legs, tuberculosis might receive consideration, but when there are additional signs of Kaposi's sarcoma, such as pigmentation, I think pseudoelephantiasis adds a useful confirmation.

Acnitis. Presented by DR. EDGAR ROLLAND BEIDELMAN, Bethlehem, Pa.

A. K., a white man aged 24, presents a papulopustular reddish brown eruption of the face, nose, ears and neck. The lesions vary in size from that of a pinhead to that of a pea and conglomerate over the area of the root of the nose. The patient's only complaints are a feeling of fatigue and some loss of weight. The present eruption started suddenly on Jan. 12, 1938, over the forehead; from this point it has gradually spread. A roentgenogram of the chest showed a small area of increased density over the apex of the left lung, old infiltration of both hili and a primary lesion at the base of the right lung. The blood count showed 5,900,000 red cells, 9,900 white cells, 16 Gm. (93 per cent) of hemoglobin, 47 per cent polymorphonuclears and 53 per cent lymphocytes. The urinalysis showed a trace of albumin. The tuberculin test gave positive results. Histologic sections showed a typical tuberculoid architecture—a purely endothelial type of tubercle, lymphocytes in the periphery and numerous giant cells of typical Langhans structure.

DISCUSSION

DR. CARROLL S. WRIGHT: This disease constitutes a difficult therapeutic problem. At the meeting of the New York Dermatological Society on April 26 it was decided in a case of similar involvement that the best policy was to let the condition alone, as in many instances it seemed to undergo involution with time.

Colloid Acne (Colloid Degeneration in Lesions of Acne). Presented by DR. SIGMUND S. GREENBAUM.

M. C., a white woman aged 30, presents several disappearing active lesions of acne and a dozen or more pinkish red macules on each cheek which were the sites of former lesions of acne. When rubbed, these become redder. They have an apple jelly-like appearance under diascopic pressure and present a soft spongy sensation on palpation. The patient has had "pimples" since the age of 14, but only a few at a time until several months ago, when a marked outbreak occurred. She used to squeeze the pus out until recently. She noticed that the remains of each lesion would take a long time to disappear.

DISCUSSION

DR. FRED D. WEIDMAN: It would be easy to regard this condition as Lewandowsky's tuberculid. When the word "colloid" is used, one thinks of something yellow, but these lesions are not yellow. The term "colloid" pertains to the translucent gluelike gross appearance and not to the microscopic picture. There is a real chance for confusion in this situation when the term "colloid acne" is used, and the members ought to realize that the condition is not colloid in the sense of colloid degeneration of the skin but is simply a hyalinized scar which looks so translucent that the word "colloid" meaning gluelike is used.

DR. SIGMUND S. GREENBAUM: I want to call attention to the fact that in this type of acne the lesions under pressure really look like lupomas. The condition is not so rare as textbooks would have one believe. The lesions have a reddish

yellow tint and feel soft when palpated gently. On puncture a drop of blood and sometimes mucoid material comes out of them; this must be expressed before the lesion will heal rapidly.

A Case for Diagnosis. Presented by DR. CARROLL S. WRIGHT.

E. C., a white woman aged 37, presents, scattered over the left side of the chest, pinhead-sized slightly inflammatory papules of a brown color which persists under diascopic pressure. Two years ago a "rash" appeared on the left side of the chest. It has gradually spread, with no tendency to involution. Recently lesions have appeared on the face. The patient has had "gallbladder trouble."

DISCUSSION

DR. J. M. SCHILDKRAUT, Trenton, N. J.: I suggest a diagnosis of urticaria pigmentosa. When the lesions are rubbed, they become elevated.

DR. JOHN H. STOKES: I agree with that diagnosis. In white women in middle life one sees at first a few lesions and then more, with gradual extension. They respond to pinching with an urticarial reaction, and biopsy will disclose an unusual number of mast cells.

DR. FRED D. WEIDMAN: I suggest a diagnosis of acne urticata in this case. Careful examination of those lesions will show an extremely minute vesicle or pustule on the summit, the same kind of lesion that occurs in straw itch. Dr. Klauder and I presented 2 cases of this disease at the 1938 Annual Session of the American Medical Association, in 1 of which there was associated polycythaemia vera.

DR. SIGMUND S. GREENBAUM: My original diagnosis was urticaria pigmentosa. Rubbing of a portion of uninvolved skin produces a marked response, with a certain amount of the dermographism in both the lesions and the surrounding skin. The question in my mind is whether a definite diagnosis can be made clinically and whether an abortive form or early stage of macular atrophy can be excluded entirely. I have seen early lesions of macular atrophy which have this reddish tint. Personally, I believe the disease is an adult form of urticaria pigmentosa.

DR. JOHN H. STOKES: There was a time when a definite distinction was drawn between urticaria with pigmentation and true urticaria pigmentosa; the difference was largely in the presence of mast cells, and the urticaria with pigmentation was perhaps the chronic form of so-called British chronic papular urticaria of adults. In the latter form there would be urticarial reactions from the most chronic and long-standing lesions, which would disappear and be replaced by others. I concluded that the condition in this case does not really belong in that classification, because the lesions of urticaria with pigmentation are much more extensive.

Fox-Fordyce Disease of Unusual Distribution. Presented by DR. REUBEN FRIEDMAN.

R. B., a white woman aged 20, shows both axillas dotted with innumerable firm pinhead-sized pinkish-violaceous papules, a few of which are capped with a central horny plug and some of which are also pierced by a hair. Similar papules are scattered discretely over the anterior wall of the chest, most abundantly over the lower part of the sternum. Over the left scapular region are some three or four papular lesions, apparently of the same type as those found in the axillas and between the breasts. The hair in both axillas is of less than normal amount. Marked keratosis pilaris involves all of both shins and less markedly affects the outer aspects of both thighs. The upper extremities show no similar involvement. The condition had its onset in October 1936, when the patient noticed a number of small itching papules at the lower part of each axilla and on the pubes. These

papules gradually increased in number and a year later appeared on and about the areola of both breasts. Four months ago the patient noticed that the skin of her legs was becoming harsh and dry. The case is presented because of the unusual presence of Fox-Fordyce lesions on the anterior wall of the chest and on the back and because of the associated and recently developed severe keratosis pilaris of the legs.

DISCUSSION

DR. EDWARD F. CORSON: My associates and I treated this patient with roentgen radiation at the Jefferson Medical College Hospital, using caution because she had had similar treatment prior to her admission to our institution. We tried certain glandular therapy also. The results were absolutely nil.

DR. SIGMUND S. GREENBAUM: I think it would be well to study the questions of vitamin A deficiency and of the patient's endocrine status.

Lupus Erythematosus with Involvement of the Mucous Membranes.
Presented by DR. EDWARD F. CORSON and DR. FRANK C. KNOWLES.

Book Reviews

La puberté: Étude clinique et physiopathologique. By Guy Laroche, with the collaboration of M. Boigey, E. Bompard, A. Desaux, R. Ducroquet, L. de Gennes, A. Hammel, T. Hernando, Madeleine Hirsch, J. A. Huet, H. Lagrange, E. Layani, P. Le Noir, C. Lian, G. Maranon, E. May, L. Meurs-Blatter, C. Richet, H. Simonnet and H. Welti. Paper. Price, 65 francs. Pp. 349. Paris: Masson & Cie, 1938.

In a symposium on the physiopathologic aspects of puberty A. Desaux contributes a chapter of forty-seven pages on the cutaneous reactions at the age of puberty. A first section is devoted to the normal development and appearance of the skin at puberty. Much stress is laid on the normal role of the endocrine glands in the development of the pilose, sebaceous and sudoriferous systems. The action of each individual gland and its hormones is considered, as well as their interrelation. In the pathologic cutaneous reactions at puberty, such as seborrhea, comedos, acne vulgaris, hypertrichosis and alopecia, Desaux is convinced that dysfunction of one or more of the endocrine glands plays an important etiologic role. The author states that he has observed several instances of the coexistence of seborrhea with precocious puberty, hyperthyroidism and gigantism and presents a number of clinical histories supporting his theory. The advent of the allergic dermatoses at puberty is ascribed to a decided activity of the reticuloendothelial system. The author believes that psoriasis frequently appears in the adolescent, and that it is due to an ultravirus developed from such occasional causes as traumatic, toxic or infectious agents on a predisposed cutaneous field, which predisposition might in turn be due to some morbid alteration of the hormones of puberty, particularly those of the hypophysis and ovaries.

Behind the Syphilis Campaign. By Philip Broughton. Price, 10 cents. Pp. 31. Public Affairs Pamphlet 24. New York: Public Affairs Committee, 1938.

This pamphlet, by a man until recently of the United States Public Health Service, represents an authoritative and valuable summary of the present nation-wide program for control of syphilis. In simple terms and convenient form are presented the genesis and background of public health efforts at reduction and ultimate eradication of syphilis in this country, a brief description of the clinical aspects of the disease and a more elaborate discussion of the significance of syphilis to the individual, to the community and to industry. This pamphlet will be found useful to nurses, school teachers, social and welfare workers and others engaged in public health education.

The Surgeon General of the United States Public Health Service has only recently appealed in the ARCHIVES to the specialists in dermatology and syphilology for assistance in the program for control of syphilis. The trinity of education, medication and legislation requires as much support for the first as for the second from the syphilologist. Those readers who have occasion to speak on the control of syphilis, either to professional or to lay audiences, will find these pages an invaluable source of useful information.

Yaws (Frambesia Tropica). By H. D. Chambers. Pp. 169, illustrated. London: J. & A. Churchill, Ltd., 1938.

The main facts concerning the clinical and epidemiologic features of yaws are well presented in this little book. The author has had wide experience with the disease and was for a time one of the medical officers of the Jamaica Yaws Commission.

An interesting account is given of the history of yaws and the possible connection of this disease with the appearance of syphilis in Europe at the end of the fifteenth century. The clinical course of the disease is adequately described, and sections are devoted to a discussion of the relation of yaws to syphilis.

Perhaps the best part of the book is that on the epidemiology of the disease. While yaws is largely confined to the tropics, its distribution even in the same tropical country is by no means uniform. The epidemiologic facts observed in Jamaica are presented in some detail, and the significance of these findings is discussed.

There is an extensive bibliography. Curiously, references to many of the original publications of the Jamaica Yaws Commission, on which much of the material in this book is based, are omitted.